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A HISTORY OF RHEUMATIC FEVER*

GORDON MANSON, M.D.**

"There is perhaps no serious disease more familiar to us than acute articular rheumatism; it is one of the disorders most commonly seen in the wards of a general hospital; it is constantly encountered in private practice; and I must confess that when I chose rheumatism as the subject of the lectures you have done me the honour to ask me to deliver, I was almost afraid that it might be deemed too trite and commonplace, destitute of sufficient novelty and interest. But there is a certain advantage in treating of a matter with which the audience are familiar, and I trust I shall be able to present it to you in some new aspects, and to attract attention to certain points of great interest hitherto, I think, insufficiently considered, and thus I hope that my choice may be justified, and any unfavourable criticism in this aspect eventually disarmed".

I regret to say that this introduction is not original with your speaker but rather is the introduction of Dr. W. B. Cheadle to his Harveian lectures for the year 1889[1]. These lectures by Dr. Cheadle are of particular significance in the history of the development of our thinking regarding rheumatic fever and we shall speak more of them later. Suffice it to say, however, Dr. Cheadle's introduction is a fitting prologue to our consideration this evening of the evolution of our concept of the rheumatic state.

The word rheumatism, of course, derives from the Greek *'pew* and refers to the flowing of humors into the joints of affected persons. Rheumatism is a disease well known to medical antiquity and one of the earliest historical accounts we have of the condition is attributed by Guillaume Baillou[2] in 1616 to Hippocrates whom he quotes as follows: "In those in whom pains and swellings come and go around the joints, and these not after the manner of gout in the foot, one will find large viscera and in the urine, a white sediment . . . Now this disease occurs in those in childhood and youth who were wont to have nose-bleeding but have since lost it". In the second century after Christ that astute clinical observer Aretaeus[3] noted — "In many cases the gout has passed into dropsy and sometimes into asthma, and from this succession there is no escape". Here he refers to those unfortunate rheumatics with chronic heart disease and congestive failure before the days of the fox-glove. We should remember that early physicians did not differentiate clearly between what today we know as rheumatism and gout. Aretaeus' clinical acumen is not confined to rheumatism for we had the opportunity last year of hearing from Fred Whitehouse[4] of his contributions to our knowledge of diabetes. We should also remember that he was the first to describe the flaring of the ala nasi and expiratory grunt seen in the lobar pneumonia patient. Finally to Aretaeus belongs the credit of being the first to note the great importance of a positive family history in the diagnosis of the acute rheumatic state. Some 1700 years have elapsed since his contributions and we are

*Presented before a meeting of the Henry Ford Hospital "2.11 Club" on May 4, 1959.
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still faced with the problem of trying to prevail on house officers and staff physicians to take an adequate family history from the acute rheumatic fever patient. About the same time Celsus[5] noted that, " . . . children in whom there has been nose-bleeding, which has ceased are sure to be troubled by pains in the head, or they have some severe joint ulcerations, or they also become debilitated by disease".

Not much is found in the medical literature from the second or third century until the observations of Guillaume Baillou in 1616. Baillou is remembered chiefly for his original description of pertussis in 1578[6] but in 1616 made the following significant observations about the two principal clinical types of rheumatic fever: "Two kinds of persons experience teaches are attacked especially by this affection — one of them healthy seen in the fullness of health but soon attacked by the disease; when now this disease attacks, a spontaneous lassitude precedes it and the blood is diseased, and indeed this is found to be the case, as was noted by Hippocrates — they are obviously sick as soon as they are attacked. The other kind of persons usually attacked by this affection are those who at the time are really sick, indeed especially with a chronic disease, which has now desisted or seems dissolved by a false and hasty crisis, but however it survives and is not destroyed — the case of Pres. Greyotte demonstrates this, whom this type of disease attacked most severely".[2] Thus we see that in the early 17th century it was appreciated that rheumatic fever might present not only as a severe acute illness but also be seen as a subtle, insidious, low grade inflammatory process eventuating in the type of patient whom we occasionally see in the height of young adulthood with a tight mitral stenosis in the absence of a history of acute rheumatic fever.

Thomas Sydenham[7] was apparently the first to note that acute rheumatic fever usually follows an acute respiratory infection. He wrote: "The sad list of symptoms begins with chills and shivers; these are followed immediately by heat, disquietude, thirst, and the other concomitants of fever. One or two days after this (sometimes sooner) the patient is attacked by severe pains in the joints, sometimes in one and sometimes in another, sometimes in his wrists, sometimes in his shoulder, sometimes in the knee — in this last joint oftenest. The pain changes its place from time to time, takes the joints in turn, and affects the one that it attacks last with redness and swelling. Sometimes during the first days, the fever and the above named symptoms go hand in hand; the fever, however, gradually goes off whilst the pain only remains; sometimes, however, it grows worse. The febrile matter has, in that case, been transferred to the joints".

In 1686 Sydenham described the chorea minor which bears his name but did not associate it with the rheumatic state. The popular eponym, St. Vitus' dance, applied to this manifestation, interestingly, derives its name from a fancied resemblance of patients so afflicted to a dancing mania seen amongst young people smitten with religious fervor in the early 15th century in the Strasbourg area of Alsace. History records that the chief magistrate of that community ordered those persons so affected to St. Vitus' chapel in Zabern in Alsace.[8] Today we note with interest that our patients may know what St. Vitus' Dance is and yet have no knowledge of the word "chorea" when we take our clinical histories.

Scarlet fever, which later came to be associated etiologically with the onset of acute rheumatic fever, was described by Daniel Sennert (1572-1637) of Breslau, Germany. Major[9] states that the existence of the disease as a clinical entity was probably suggested to Sennert by his brother-in-law Döring. Sennert was a conscientious and devoted physician. Six times epidemics of plague invaded his city and because of fear of the disease, most of the physicians in the city fled. Sennert was one of the few who invariably remained to care for his people and as a consequence died of plague when the 7th epidemic raged through his community. It remained however for Sydenham to clearly differentiate the clinical courses of scarlet fever and measles which had hitherto been confused. According to Lettsom,[10] Sydenham died a "martyr to the gout". In the way of therapy Sydenham is remembered for his emphasis on the clinical uses of quinine though he did not make particular reference to the use of this drug in the rheumatic state. 200 years were to elapse before the clinical usefulness of antipyretics in the rheumatic state would be appreciated.

With the rise of pathologic anatomy in the early 18th century, inevitably descriptions of rheumatic lesions began to appear. Valvular vegetations were first noted by Lancisi,[11] a papal physician in the year 1709 who published autopsy findings. Similar findings were later published in 1761 by Morgagni.[12] A year previously Anton Störck[13] of Vienna, a pharmacologist and student of the famous pathologist Boerhaave, described the autopsy findings of pleural and pulmonary lesions in acute rheumatic fever. In 1761 Richard Pulteney[14] an English pharmacist, provided an excellent description of rheumatic heart disease at autopsy without recognizing the nature of the disease. In the latter part of the 18th century, various clinical and pathological observations began to be correlated which served to relate the acute rheumatic state as seen clinically with organic heart disease seen at autopsy. In 1776 William Cullen,[15] Professor of Pharmacology in Edinburgh, pointed out that rheumatic joints never suppurated. Lettsom,[16] a biographer of Sydenham, reported what appears to have been the thrill of mitral stenosis in the following graphic terms: "Upon laying the hand on the sternum, it gave a sensation to the touch — somewhat like a fluid passing through a cylinder, in the central substance of which a ball had been infixed, against which the impulse of the circulating fluid had been directed, and by it repelled with a vibratory motion along the cylinder".

Edward Jenner[17] in July 29, 1789 addressed the Fleece Medical Society on a disease of the heart following acute rheumatism, illustrated with dissections. This paper was never published and has apparently been lost. One finds no reference to its content in the literature. Our only knowledge of its existence comes from the fact that in 1805 Jenner wrote to a Dr. Parry regarding a friend's death and in this letter referred to the paper and requested its return. So far as is known the paper was never returned. Matthew Baillie, whose text on Morbid Anatomy[18] contained some of the finest pathological plates printed up until that time, in 1797 stated in his text, "the causes which produce a morbid growth of the heart are probably not all of them ascertained. The chief causes are ossification or thickening of some of its valves. On some occasions the heart will become enlarged from rheumatism attacking it". Baillie appended a footnote to this observation as follows, "Dr. Pitcairn observed this

in several cases and is to be considered as the first person who made this important observation". (The observation was made in 1788 by Pitcairn). The career of Matthew Baillie as a physician and pathologist deserves further comment. He was the last of a quartet of famous English physicians immortalized in "The Gold Headed Cane". These men — Mead, Askew, Pitcairn and Baillie were successive owners of the Gold Headed Cane signifying professional leadership in 18th century and early 19th century London. When Baillie died, his widow presented the Gold Headed Cane to the Royal College of Physicians in whose museum it still resides as a tribute to the medical acumen of these great clinicians.[9]

John Haygarth[19] in 1805 made the significant observation that acute rheumatic fever is not always accompanied by fever and stated: "The term rheumatism, both in common and medical languages includes a great variety of disorders, which ought to be distinguished from each other by different names. After separating it from the nodosity of the joints, tic douloreux, sciatica, lumbago, and other diseases which the nosologists have placed under this classification, there still remain 470 cases of rheumatism. This disease is generally classed with fevers, and yet only 170 (about one-third of them) had any fever". With this introduction, Haygarth then discusses the clinical description and course of the disease. He was among the first to find Peruvian Bark excellent in the management of rheumatic fever though Sydenham had earlier appreciated its symptomtic effects in a variety of disease states.

The early 19th century was punctuated by a variety of climatological and epidemiological observations, largely speculative in character. In this period we also see contributions regarding various manifestations of the rheumatic state. In 1810 William Wells[9] described rheumatic nodules. Wells' background was interesting from an historical point of view. He was born in Charleston, South Carolina of staunchly Loyalist parents and as a child his father dressed him in a blue coat lest he be mistaken for an American. His education was largely English and in his younger days he made a number of contributions as a physicist and his "Essay on Dew" was read before the Royal Society in 1814. A year earlier he had proposed a theory of natural selection which antedated by some 40 years the publication of the "Origin of Species" by Charles Darwin. This priority of Wells was acknowledged by Darwin in his classic volume. In describing rheumatic nodules in regard to a 15 year old girl he states: "many of the tendons of the superficial muscles of this patient were studded with numerous small hard tumors, an appearance which I have observed only in one other person, a thin and feeble man forty-one years old, who also labored under rheumatism".

The association of rheumatism and chorea is attributed to Thomas Addison of Guy's Hospital, by Babbington to whom we are indebted for the development of laryngoscopy.[11] The importance of myocarditis and its preponderance in the pediatric age group was noted by Robert Adams[20] of the Jervis Street Hospital, Dublin, in 1827. It was later re-emphasized by Sturges[21] in 1876 whose name is perpetuated in the Kalischer-Sturges-Weber-Dmitri Syndrome, to give it its full and historical appellation. Another Guy's Hospital physician, Richard Bright[22] in 1831 described what he termed

roseola annulata as a manifestation of the rheumatic state, and in 1835 Thomas Watson[23] stated: "I confidently believe the to and fro sound to be always indicative of inflammation of the external membrane . . . the blowing sound to be always indicative of inflammation of the internal membrane of the heart". We might today take issue with Watson regarding the interpretation of abnormal heart sounds but we must acknowledge his important observation regarding the age distribution of the cardiac and arthritic manifestations of the rheumatic state which he expressed as follows: "One law respecting the connection between the cardiac and the arthritic symptoms may be stated with confidence, namely, that the younger the patient who suffers acute rheumatism (and I have seen it as early as the third or fourth year) the more likely will he be to have rheumatic carditis. The chance of this combination appears to diminish after puberty as life advances". Interestingly enough, we probably owe the term "Waterhammer Pulse" to Watson rather than to Corrigan since Corrigan, in his description of the collapsing pulse of aortic insufficiency, does not use the term Waterhammer Pulse.[11]

During the 18th century various theories were proposed regarding the pathogenesis of the rheumatic state. One of the earliest was suggested by Baron Corvisart[24] who was Napoleon's physician. It was the Baron's suggestion that rheumatic valvular vegetations were internal manifestations of venereal warts. Whether this is a serious hypothesis or is a consequence of the inclinations and habits of the French army is open to conjecture. In 1827 William Prout,[11] an English chemist, found elevation of blood lactic acid and suggested that a disturbance in this metabolite was responsible for the rheumatic state. His methods are not available to us and it is interseting to consider what accounted for the increase in blood lactic acid he observed. It is entirely possible that it may have been due to congestive failure which has been observed to produce an increase in blood lactic acid level in terminal patients following unsuccessful cardiotomy. It may also have been due to unrecognized cases of Pompe's disease. During the middle 18th century the idea that the rheumatic state was a consequence of an increased blood uric acid level was popular until A. E. Garrod[11] demonstrated that the uric acid level was normal in acute rheumatic fever patients. Garrod later distinguished himself by giving us the concept of inborn errors of metabolism. In 1861 Armand Trousseau,[25] who is known for the sign of tetany which bears his name, pointed out the temporal relationships of rheumatic angina (i.e. tonsillitis) to subsequent acute rheumatism.

The major contribution, and indeed our modern concept of the rheumatic state, was proposed by W. B. Cheadle in the Harveian lectures for the year 1889.[1] Dr. Cheadle himself was a remarkable individual.[26] He was the co-author of a book on explorations in the Canadian Rocky Mountains which he undertook before embarking upon his medical career. His explorations took place in the 1860's at a time when travelers in the area stood a good chance of having their scalps lifted by any of the several techniques described to us a couple of years ago so capably by our late colleague, Dr. Robert Clifford.[27] Cheadle's interests and original work lay in the area of measles, infant feeding, heart disease, cirrhosis, Grave's Disease and he was one of the first to separate infantile rickets and scurvy. He had a deep personal interest

in the rheumatic state for his appreciation of the importance of family history was heightened by the fact that his wife and son suffered from rheumatic fever. Oddly enough he made no original contributions to our knowlegde of the rheumatic state but in the matter of a very few years became known throughout the world as an expert on rheumatism as a consequence of his Harveian lectures. This was further insured by his authorship of the section on rheumatic fever in Keating's "Cyclopedia of Diseases of Children," published in Philadelphia in 1890 which was the standard American pediatric text of the day. Cheadle took the various divergent manifestations of the rheumatic state and put them together for us in a neat pathogenetic package which has remained unchanged to the present time. He appreciated the fact that the manifestations in childhood differ from those in adulthood and that childhood manifestations are followed by adult manifestations as the individual grows older. American and British pediatricians in the early part of the present century all learned what was termed "Cheadle's Cycle" consisting of: endocarditis, pericarditis, pleurisy, exudative erythema, chorea, nodules and tonsillitis. He recognized the predilection of the disease for connective tissue and pointed out that usually two or three phases occurred together. The major and minor criteria proposed by the late T. Duckett Jones[28] do not differ from this concept. He found that the disease had a familial tendency as strong as gout and remarked that our appreciation of this, "varies according to the minuteness of the inquiry made". His discussion of chorea is illuminating to the pediatrician today. He shrewdly noted that the transient nature of other rheumatic manifestations in the chorea patient are often evanescent enough to be easily missed and hence chorea is thought to be of non-rheumatic origin. He reminds us that Roger, whose name is not unknown to us, pointed out that chorea usually preceded the later development of arthritis and he states in conclusion that, "I do not think the evidence warrants the assumption that chorea is inevitably of rheumatic origin . . . but I am convinced that rheumatism is the most common and potent factor". I do not believe that the question of the etiology and pathogenesis of chorea has progressed much since. Cheadle clearly differentiated clinically between innocent and organic murmurs and laments the impossibility of obtaining adequate data on rheumatic patients for statistical analysis. Here he finds himself in company with Thomas Barlow to whom we owe our knowledge of the pathogenesis of infantile scurvy. That cardiac hypertrophy and dilatation without valvular disease can occur in the acute rheumatic fever, Cheadle pointed out, was recognized in 1881. He noted that Henoch's "Diseases of Children" in 1883 stated that post scarletinal endocarditis and pericarditis may be of either rheumatic or uremic origin and hence we see two important manifestations of streptococcosis may both lead to carditis but by entirely different means.

Cheadle lived in a remarkable period in pediatric history. He was contemporary with Barlow known for his work in scurvy, Garrod who gave us the concept of inborn errors of metabolism, Thomson whose contribution to the care of the brain damaged child represented a new concept in the understanding of these children and with Still whose disease bears his name today.[29] Cheadle's differential diagnosis of the child who presents with acute arthritis is interesting when compared with a similar differential diagnosis published in 1958 by a rheumatism center in England:[30]

Cheadle's Differential Diagnosis	The Rheumatism Research Unit Taplow, 1958, 196 patients
a. Leutic epiphysitis	1
b. Scurvy	0
c. Rickets	0
d. Tetany	0
e. Hemophilia	2 (blood dyscrasias)
f. Tuberculosis	2 (pulmonary only)
g. Pyarthrosis	10

The differences in the above disease distribution represent some 70 years of Pediatric progress. The virtual disappearance of Lues is a tribute to prenatal blood testing and the efficacy of Fleming's penicillin. The complete disappearance of the nutritional diseases, scurvy, rickets and tetany are a clear reflection of improved infant feeding. In the field of two of these nutritional disorders Cheadle himself made original contributions together with Barlow. Blood dyscrasias remains with us as always. Tuberculosis is still seen in a small but significant number of cases, more frequently today in England than in the United States. It might be remembered in passing that in the United States we have never as a nation embraced BCG vaccination. Finally, pyarthroses remain with us and the causative organisms remain much as they were in Cheadle's time, despite current concern over the ubiquitous staphylococcus.

Some six years after Cheadle's remarkable Harveian lectures, the first epidemiological study of the disease was summarized in the Milroy Lectures by Sir Arthur Newsholme[31] in the year 1895. These are published in Lancet for the same year. His data was the result of a cooperative study and a number of important conclusions were reached regarding the epidemiology of rheumatic fever. Essentially the same tendencies were found by Coburn in the 20th century. Newsholme showed that the disease was one affecting individuals in temperate climates. It was shown that the affected individuals had an inherited predisposition to their disease thereby confirming the observations of Aretaeus in the second century. Frequently stress, in the form of fatigue, chill or injury precipitated acute rheumatic activity, foreshadowing by some 40 years, the observations of Selye. Certain years were observed in which there appeared to be epidemics of acute rheumatic fever usually following a sore throat. These observations were later confirmed, of course, during World War II in the armed forces. Then tendency of acute rheumatic fever to recur was well established by Newsholme. He concluded that the disease was probably caused by an organism of low infectivity which tended to be concentrated about the joints and was probably a saprophytic organism which could on occasion become parasitic. This latter conclusion represents the one false note in these Milroy lectures on rheumatic fever in the light of our knowledge of the disease today. It was not until the second decade of the 20th century that the concept of hypersensitivity was suggested as a mechanism of pathogenesis. Nine years after Newsholme gave the Milroy lectures, Ludwig Aschoff[32] in 1904 reported the histologic characteristics of the lesion we have come to associate as the essential criterion of acute rheumatic activity, the Aschoff Body. His description of this important lesion is quoted at length since it is found that our current textbooks of pathology suffer by comparison:

"We find peculiar nodules, which appear to be specific to rheumatic myocarditis. These regularly occur in the neighborhood of small or medium sized vessels and most frequently in the vicinity of the adventitia, or there existed simultaneously a disease of all of the vascular layers, such as is described in arteritis nodosa. The nodules are unusually small, mostly submiliary, and originate by the conglomeration of large elements, with one or more abnormally large indented polymorphic nuclei. Arrangement of the cells frequently occur in the form of a fan or rosette. The periphery is formed by the large nucleus, the center by the paler, necrotic mass of confluent cell protoplasm . . . small and large lymphocytes and polymorphonuclear leukocytes force themselves a short distance between the large cells of the periphery or form a peripheral zone, and irregular projections from these may extend far into the connective tissue partitions. In these projections . . . are found giant cell-like large nucleated elements appearing singly or collected in nodules . . ."

With the coming of the 20th century, many different etiologic theories began to appear in rapid succession.[33] Various organisms were reported as etiologic organisms because they had been isolated from a fair number of rheumatic fever patients. In no instance, however, were Koch's postulates fulfilled with any of the various organisms reported in the literature. Poynton and Paine isolated a strain of streptococcus viridans which met an unhappy fate when it was blown up by German bombing in World War I. Birkhaug recovered a hemolytic streptococcus. Small reported an organism he termed streptococcus cardioarthriditis in 1928. Swift suggested the role of hypersensitivity in the production of the rheumatic state and this was soon supported by Faber and Zinsser. Schlesinger, Sabin and others in the early 1930's demonstrated that certain particles could be agglutinated by the sera of rheumatic fever patients and felt that was supporting evidence for a viral etiology of the disease. In 1935 Rinehart suggested the role of Vitamin C in the production of acute rheumatic fever. Certainly an important contribution to our knowledge of the rheumatic state was made by Coburn[34] who published his study on the factor of infection in the rheumatic state in 1931. Like others before him, he emphasized the variability of the disease. It is interesting to those of us who are Pediatricians to note his description of the pulmonary hyaline membrane at autopsy which we have come to think of as an exclusively primary neonatal phenomenon, which it clearly is not. Coburn's major contribution to our knowledge of the rheumatic state consisted of transporting a group of known rheumatic fever patients from New York City, where the streptococcus was frequent, to Puerto Rico, where the streptococcus was infrequent, for a period of 6 months. In the relatively streptococcus-free atmosphere of Puerto Rico, these children experienced a gratifying regression of their rheumatic activity and a large proportion returned to a state of physical health. However, when these children were returned to New York City, a significant proportion experienced a recrudescence of rheumatic activity. Coburn also carried out some interesting skin tests with bacterial nucleoproteins from various organisms, not all of which were streptococci. In some individuals these skin tests produced interesting and rather startling results. Unfortunately the results were not consistent regarding the streptococcus in these rheumatic susceptible individuals. Certain rather disturbing reactions were seen—among them; the development of generalized erythema marginatum, the development of rather extensive purpuric

reactions, the appearance of rather deep sloughs and the appearance of nodular erythema. Coburn felt four factors were involved in the production of rheumatic fever symptomatology which he stated as follows; inherited susceptibility, age, environment and infection. It was concluded that rheumatic fever represented a special tissue response to upper respiratory disease and that the streptococcus was an important contributory factor.

No historical consideration of the rheumatic state would be complete without an account of the curious and interesting history of the use of salicylates in this disease. We recall that in 1805 John Haygarth found Peruvian Bark excellent for the symptomatic treatment of the condition. In 1827 Leroux isolated the glycoside salicin from Willow Bark. In 1838 Leroux obtained his salicin from the ordinary white willow (Salix alba) found in Europe. Piria isolated salicylic acid in 1838. He hydrolyzed salicin which yielded glucose plus salicylic acid. Not much was done in an investigative way until Thomas MacLagen[35] in 1874 observed that rheumatic fever was "apt to occur in low-lying, damp localities . . . and was of miasmic origin", MacLagen felt that the disease was allied to, but distinct from malaria. He reasoned that since Cinchona bark was of value in malaria and was an extract of a bark indigenous to the area in which malaria occurred, it was therefore only logical to seek a bark from the native areas where rheumatic fever occurred to find a drug suitable for the treatment of rheumatic fever. Hence, the bark of the willow, and its extract salicin, should logically be used in the management of acute rheumatic fever. These observations were published in Lancet in 1876 and the suggestion was immediately accepted by the medical profession and so salicylates have continued to be used to the present day for the treatment of rheumatic symptomatology.

Interestingly enough, however, the train of thought noted above is not the only one which led to the development of the very useful drug we know today as aspirin.[36] In 1865, Joseph Lister conceived his idea of antisepsis through the use of a carbolic acid spray and this work was published in Lancet in 1867. It was followed by the attempt in 1874 of Herman Kolbe, a professor of chemistry in Leipzig, to produce salicylic acid for use as an antibacterial agent with the idea in mind that it was a phenol derivative which could be given by mouth. A little clinical experience soon showed that salicylic acid produced only symptomatic relief and its antipyretic and analgesic properties became well defined. Franz Stricker in Berlin found salicylates were effective in the treatment of rheumatic fever, rheumatoid arthritis, neuritis, neuralgia and headache, thereby antedating our current television advertisements by some 85 years. Clinicians of the time found the gastro-intestinal side effects of salicylic acid and sodium salicylates were quite troublesome. This undesirable side effect of the drugs stimulated a Bayer chemist, Felix Hoffman, whose father had rheumatoid arthritis, to search out acetyl salicylic acid which he found about 1880. Actually this compound had been synthesized in 1853 by Charles Von Gerhardt and nothing further had been done with the material. It remained for almost thirty years a laboratory curiosity. At Hoffman's suggestion, clinical trails of acetyl salicylic acid were conducted by Heinrich Dresser, Bayer's pharmaceutical research chief, who found it useful clinically. It was he who termed the material aspirin since natural salicylic acid came

from plants of the spiria family and because it was also known as spiric acid, the acetyl derivative might logically be called aspirin and so we have the name which persisits today. In reviewing the literature of the time, one can infer, I think, that clinicians of the period not infrequently encountered salicylism in patients under treatment. Some of us may recall such patients in our own practices. Cheadle, in his memorable monograph, suggests the advantages of the administration of alkalis to patients who are receiving salicin. Today we are biochemically aware of the ability of alkali to enhance the renal excretion of salicylates.

The commercial aspects of acetyl salicylic acid are not without interest. Quite naturally, the Bayer Company took full patent advantage of the work of Hoffman, Von Gerhardt and Heinrich in producing aspirin as a clinically useful drug. The firm held exclusive rights for the commercial production of the material until the expiration of the American patents in 1917. Anticipating this, the Monsanto Chemical Company sent Dr. Gaston Dubois to Switzerland where he purchased rights to a process for the cheap and efficient commercial production of the compound and with the expiration of Bayer's American patents, Monsanto immediately went into production. Extensive litigation followed which ended in the year 1919 with the Bayer Chemical Company losing the judgment. In that year, the Monsanto Chemical Company produced 480,874 pounds of acetyl salicylic acid. By 1956 the Monsanto Chemical Company had produced its 100th million pound of acetyl salicylic acid and an excellent history of the drug was given by Dr. Carroll Hochwalt of the Monsanto Company in the fall of 1956 at a Symposium on Aspirin Research. This address is printed in the Journal of Pediatrics of the year 1957 and is well worth reading in its entirety.

With a review of the fascinating history of that most useful drug, aspirin, we shall conclude consideration of the history of the development of our concept of the rheumatic state. Many of those present this evening are more intimately familiar with the details of the development of the potent steroid hormones than is the speaker. In a sense, steroids are still in the process of making medical history. While we know they are effective in ablating rheumatic symptomatology, we do not have sufficient experience with them nor have we observed patients so treated for a sufficient period of time to determine their ultimate long term effect on the rheumatic individual. Moreover, after eleven years we are still not fully acquainted with their widespread and subtle metabolic effects. Then too, the drug houses continue to add confusion by producing synthetic steroids at an alarmingly rapid rate, the actions of which have never been previously inflicted on the human organism. Possibly in twenty years another T. Duckett Jones will appear to assay adequately that which we do today.

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GONADAL DYSGENESIS (TURNER'S SYNDROME) WITH ASSOCIATED LIVER DISEASE AND BLEEDING ESOPHAGEAL VARICES

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In 1938, Turner[1] described a triad of infantilism with webbing of the neck and deformity of the elbow (cubitus valgus) in seven female patients. Their breasts, vaginae and uteri were infantile and menstruation had not occurred. In 1942, Varney, Kenyon and Koch[2] described four young women with short stature and retarded sexual development who had high titers of urinary gonadotropin. This latter finding obviated hypopituitarism as the cause of the observed sexual infantilism. In the same year Albright et al[3] reported on "primary ovarian insufficiency and decreased stature." The frequency of associated congenital anomalies, especially webbing of the neck, cubitus valgus, coarctation of the aorta, late union of the epiphyses, osteoporosis, precocious senility and hypertension have been noted by many authors. This report concerns a case of gonadal dysgenesis with associated idiopathic liver disease and bleeding esophageal varices.

CASE REPORT

(V. M., Case number 198641). The patient is a 55-year-old unmarried, white female who presented herself to the Division of Gastroenterology in November of 1958. She had felt well until 5 days previously when she developed malaise, nausea and raised "coffee ground" emesis. Her stools had become darker than usual. She denied anorexia, pain and weight loss. There had been no change in her bowel habits. Interestingly, she related that she had been amenorrheic all her life.

On physical examination she appeared extremely pale and small in stature. (Fig. 1) She appeared older than her chronological age. Her height was 59 inches. She weighed 92½ pounds. Blood pressure was 120 systolic and 80 diastolic. Her pulse was 88 per minute. Temperature was 98.6 degrees F. The patient exhibited a kyphoscoliosis and deformity of both wrists caused by previous Colles' fractures. Her skin was atrophic with several small scattered ecchymoses present. There was a trace of axillary hair and about one-third the normally expected adult pubic hair. Her body proportions appeared to be grossly normal. Breast development was infantile with poor areolar and nipple differentiation. Pelvic examination revealed an infantile vagina with a very small introitus. The ovaries and uterus could not be palpated rectally. Black stool was in the rectum. There was no webbing of the neck or valgus cubitus. Examination of the heart, lungs and abdomen was normal. Arterial spiders and palmar erythema were absent.

The patient was admitted to the hospital as a problem of gastrointestinal bleeding. The initial hemoglobin was 7.7 gm. per 100 ml. The leukocyte count was 10,000 per

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Figure 1

54 year old patient with gonadal dysgenesis. Height 59 inches. Note sparse pubic hair and premature senility.

Figure 2

Roentgenogram of distal esophagus showing esophageal varices in patient in Fig. 1.

cu. mm. The blood urea nitrogen and fasting blood sugar were normal. Gastric analysis showed normal gastric acidity. There was 12 per cent retention of bromsulphalein dye after 45 minutes. The total serum cholesterol was 200 mg. per 100 ml. with an ester fraction of 55 per cent. An electrophoretic pattern of the serum proteins revealed a total protein of 5.8 gm. per 100 ml., albumin 3.49 gm., alpha-1 globulin 0.28 gm., alpha-2 globulin 0.49 gm., beta globulin 0.94 gm., and gamma globulin 0.59 gm. The alkaline phosphatase was 7.8 Bodanski units per 100 ml. Thymol turbidity was 2 units and the cephalin cholesterol flocculation was 0. The serum transaminase (SGOT) was 19 units. The serum calcium and phosphorus were normal. A 24 hour urine for follicle stimulating hormone (FSH) was positive at the level of 64 mouse uterine units. A male sex chromatin pattern was present on a buccal smear. Roentgen examination of the gastrointestinal tract showed esophageal varices. (Fig. 2) Marked osteoporosis and kyphoscoliosis of the dorsal and lumbar spine were evident on bone x-rays. Histological study of liver tissue obtained through percutaneous needle biopsy was interpreted as showing periportal fibrosis. Fig. 3, 4)

The etiology of the patient's liver disease and esophageal varices was an enigma. She did not use alcohol and her diet had always been excellent. She was employed as a clerical worker in a business office. There was no known exposure to recognized hepatic poisons. The patient was one of 8 offspring and was the shortest sibling. Her parents were of average height. Her birth weight was 5 pounds and she reported

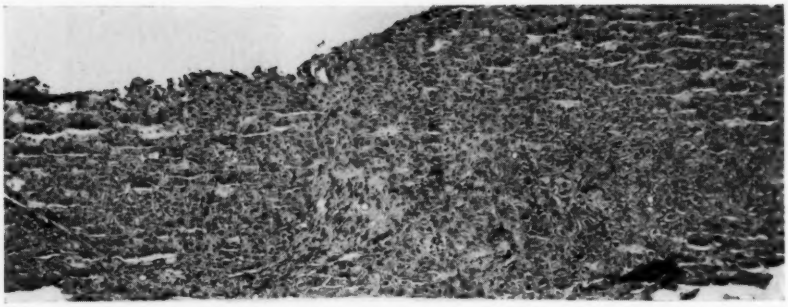

Figure 3

Liver, with an area of non-specific periductular fibrosis near center of photograph. The remainder of the liver shows no remarkable change. H & E x 70.

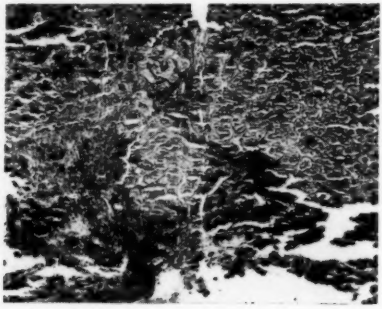

Figure 4

Liver with non-specific periductular fibrosis, producing so called pseudocirrhotic nodules near center of photograph. Trichrome x 70.

that she had always been small and did not recall any period when growth ceased. She appeared to be of average intelligence and completed high school.

The patient had been seen at this hospital 25 years previously when she was age 30. She had caught her right hand in a washing-machine wringer. Fractures were absent by roentgen studies but it was noted that there was delayed union of the epiphyses of the distal radius and ulna. A short time later the patient reappeared in the Orthopedic clinc seeking examination for low back pain which had been present for about 3 years. Spine x-rays at that time were interpreted as showing marked osteoporosis and scoliosis. The fifth lumbar verteba was slightly forward with respect to the body of the sacrum and was felt to represent prespondylolisthesis. The patient was not seen again until the above episode of bleeding from esophageal varices.

The patient received a total of 2000 ml. of whole blood during her hospitalization and her hemoglobin at time of discharge was 12.4 gm. per 100 ml. A therapeutic program consisting of diet, vitamins, oral estrogen and testosterone is anticipated.

DISCUSSION

It has been surprising and interesting that an individual with the female or male chromosomal constitution (XX or XY) may still develop into either a male or female. Animal experimentation has demonstrated that early removal or destruction of the fetal gonads leads invariably to female development of the ducts and genitalia. This observation emphasized the importance of embryonic testes in counteracting the inherent tendency of the fetus to femininize. Individuals with "ovarian agenesis" had always been considered to be genetic females. In 1950 Wilkins[4] recognizing the clinical significance of these animal experiments predicted that some patients with this disorder should be chromosomal males. The demonstration of a sex chromatin dimorphism by Barr[5] and its relative easy determination through buccal smears has established that about 80 per cent of "girls" with Turner's Syndrome are genetic males. Objection has been raised to the term ovarian agenesis inasmuch as rudimentary mesonephric elements of the gonad are present in the genital ridge. It has been suggested that gonadal dysgenesis is more descriptive than ovarian agenesis.

The separation of this syndrome from pituitary dwarfism was greatly abetted by the discovery of high urinary gonadotropin levels. Other differentiating features are: (a) The individual are short rather than dwarfs (b) The bone ages are only slightly retarded than markedly so (c) These patients have a reduced amount of axillary and pubic hair rather than none at all (d) Estrogen therapy in these individuals leads to marked increase in axillary and pubic hair whereas it has no such effect in panhypopituitarism (e) These patients are quite strong and well nourished rather than weak and undernourished (f) These patients are prone to have other congenital anomalies (g) In an insulin tolerance test these patients exhibit normal hypoglycemia as opposed to hypoglycemia unresponsiveness.

Mellinger[6] has written that the disorder is not familial and it is believed to result from an acquired defect of the fertilized ovum, with multiple developmental anomalies, including the failure of gonadal tissue differentiation. Experimental work with amphibians has shown that fertilized overripe eggs develop abnormally. Even if only mildly affected the germ plasm proves highly susceptible to the damage. Witchi et al[7] believe that germinal degradation (blastophthoria) may be the primary cause of gonadal dysgenesis. Gonadal insufficiency may be but one of a series of congenital abnormalities occuring in the same individual.

The patient in this report is interesting because of the manifest absence of the usual etiologies for her liver disease. It is possible that her liver disease is present on a congenital basis as are her other anomalies. If this were the case however, one might have expected an earlier clinical appearance of her liver disease. The liver's failure to keep circulating estrogens at a normal level has been a popular hypothesis explaining the appearance of spiders. If this notion is correct one would not expect the appearance of spiders in this patient since the major source of her estrogens is congenitally absent.

SUMMARY

A case report of a patient with gonadal dysgenesis (Turner's Syndrome) and associated idiopathic liver disease and bleeding esophageal varices is presented.

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OBSERVATIONS ON ULTRATHIN SECTIONS OF DOG LUNG BY METHODS OF ELECTRON MICROSCOPY

JOHN H. L. WATSON* AND VIRGINIA VALENTINE*

The application of ultrathin sectioning techniques to biological tissue, and electron microscopy of the sections are well known, and new references are constantly being added to the subject. However, whenever a research group undertakes a problem involving the study by these methods of any type of tissue, it must be a first task to establish the 'normal' morphology for the techniques, instrumentation and methods of that group. It was our concern to establish for this laboratory, the cytological features of control dog lung, as a preliminary aspect of a larger project involving the eventual infiltration of the vascular system of lung with ultramicroscopic crystals of alpha iron†[1], both radioactive and non-radioactive. The findings reported here agree with those determined earlier by Low[2] and confirmed and expanded by others.[3,4]

While the work of others can be taken, and should be taken as criteria to be used for comparative and interpretative purposes, one must 'see' for oneself what the tissue looks like. This attitude must be taken first with regard to the normal material, and then with regard to the pathological or experimental matter. Further, the valuable information derivable from light microscopy of the same material must be utilized, especially for orientation of the observer between the well known and recognizable structures observed at the magnifications, resolution and contrasts (colors) inherent in the light microscopy, and the same quite different magnitudes and qualities of the same quantities in electron microscopy. For instance, there is a considerable difference in the size of field observable at X900 in a light microscope and at anywhere from X900 to X10,000 or much higher in an electron microscope.

There is often appreciable confusion if one attempts to step directly from a resolution of about 1500 angstrom units in light microscopy to 50 angstrom units or better in electron microscopy with all the wealth of unexplainable and unexplained detail such images are likely to demonstrate. Coupled with this is the 'new' information derivable from the fact that in electron microscopy there are none of the usual stains or colors so well-loved of light microscopists, but everywhere there are mere shades of black and white which are a result of more or less 'staining' by the molecules of the relatively high electron scattering fixative osmium tetroxide, (or other similar compound). The contrasts may be quite divergent from the appearances expected from light microscopy.

Any observation can be made only under some set of artificial conditions. Nothing can ever be seen *à la nature*, but only under the circumstances of the observation. Ingenious attempts are made to approach nature or to simulate it, but at best these attempts fail in one aspect or another. This is a true, (although often less strikingly so) of electron microscopy as of any other method of observation, and all interpretation must be made accordingly.

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†Unique crystals of iron, as well as of others of the transition elements, notably cobalt and copper, are provided for this work by Dr. Michael W. Freeman.

The tissue is fixed as rapidly as possible because autolysis of the ultramicroscopic structures will be understandably rapid. Fixation-staining must be carefully controlled so as to produce as few artifacts as possible, and several normal runs should be studied to make certain that results are reproducible and that the fixation is such as to delineate all the structures without obscuring some or producing others which do not actually exist. Embedding must also be controlled, first to preserve the structures, second to make the cutting of thin sections possible, and finally so as to be effected uniformly everywhere throughout the block without introduction of artifacts. The tissue and the block must be trimmed and observations made eventually far enough from the area trimmed that artifacts from the trimming process itself will not be recorded as characteristic of the tissue. In the cutting, the knives must be carefully chosen and many discarded before one that is suitable is found, and often one or two cuts are enough to ruin the blade, depending upon whether a knife edge of steel, glass, or diamond is used. During the cutting and preparation of the block the room temperature must be controlled and kept a little lower than is normally comfortable, about 68°F. Ideally room and microtome vibration should be non-existent. A thin section, (the order of 1/40 microns) is striven for, but often a section which is too thin can be as useless as a one which is too thick. Setting the microtome mechanically for some desirable thickness is usually not sufficiently satisfactory, since an unexpected temperature change, an undetected vibration, or other factors may feed a little less or a little more of the block to give an undesirable result.

Mounting the section on the electron microscope grid can lead to artifacts. Water is notably dirty, even when distilled. Sections tend to fold rather than to stay flat. The formvar or carbon supporting films may be dirty, too thick, separated or broken. And when the section is finally in the electron microscope, lack of resolution due to a myriad of reasons, too numerous to be discussed here, or effects of electrons upon the section to evaporate[5], break or contaminate it must be expected, and be reduced to a minimum.

MATERIALS AND METHODS

Lung tissue was obtained from six day old dogs, killed without anesthesia by a blow on the head. The lung tissue was removed immediately to cold, buffered 1 percent osmium tetroxide solution, and left in this fixative for 2 hours after being cut into cubic millimeter pieces. Karrer's technique of dehydration with acetone was used[6]. Embedding was effected in prepolymerized *n*-butyl methacrylate. Before final polymerization, the capsules which contained the tissue in the prepolymerized monomer were evacuated and flushed with dry nitrogen, according to Moore[7]. Polymerization was completed in the Canalco embedding chamber at 80°C.

Glass knives were used to section the material with a Porter-Blum ultramicrotome, and the sections were mounted upon Formvar-coated Athene Grids. A modified EMU-2B electron microscope was used for the microscopy.

OBSERVATIONS

The electron micrographs are cross sections of the alveolar capillary tissue of the dog lung. Macroscopically, the areas represent the alveoli (Alv), or air spaces, the septum or air-blood "barriers", and the capillaries (Cap). Plate 1 shows a typical

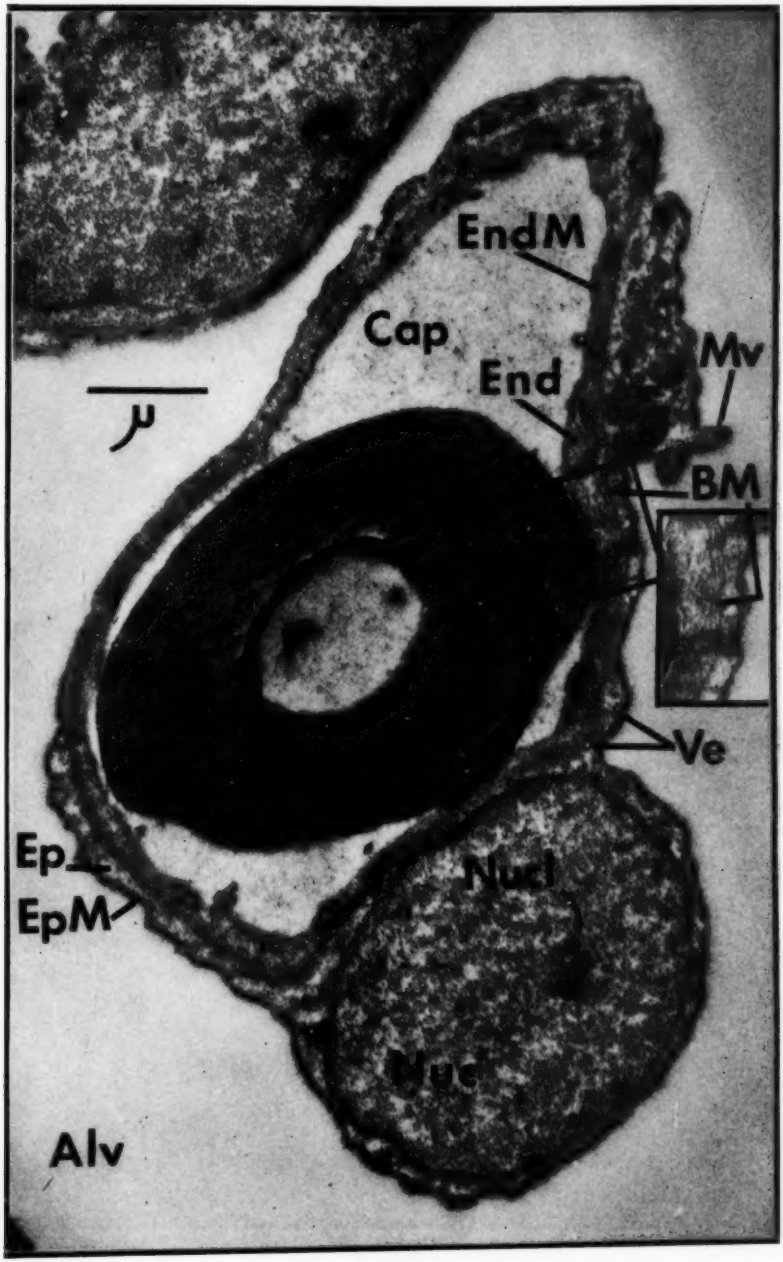

Plate 1

Puppy Lung, x19,000. Insert, x28,000.

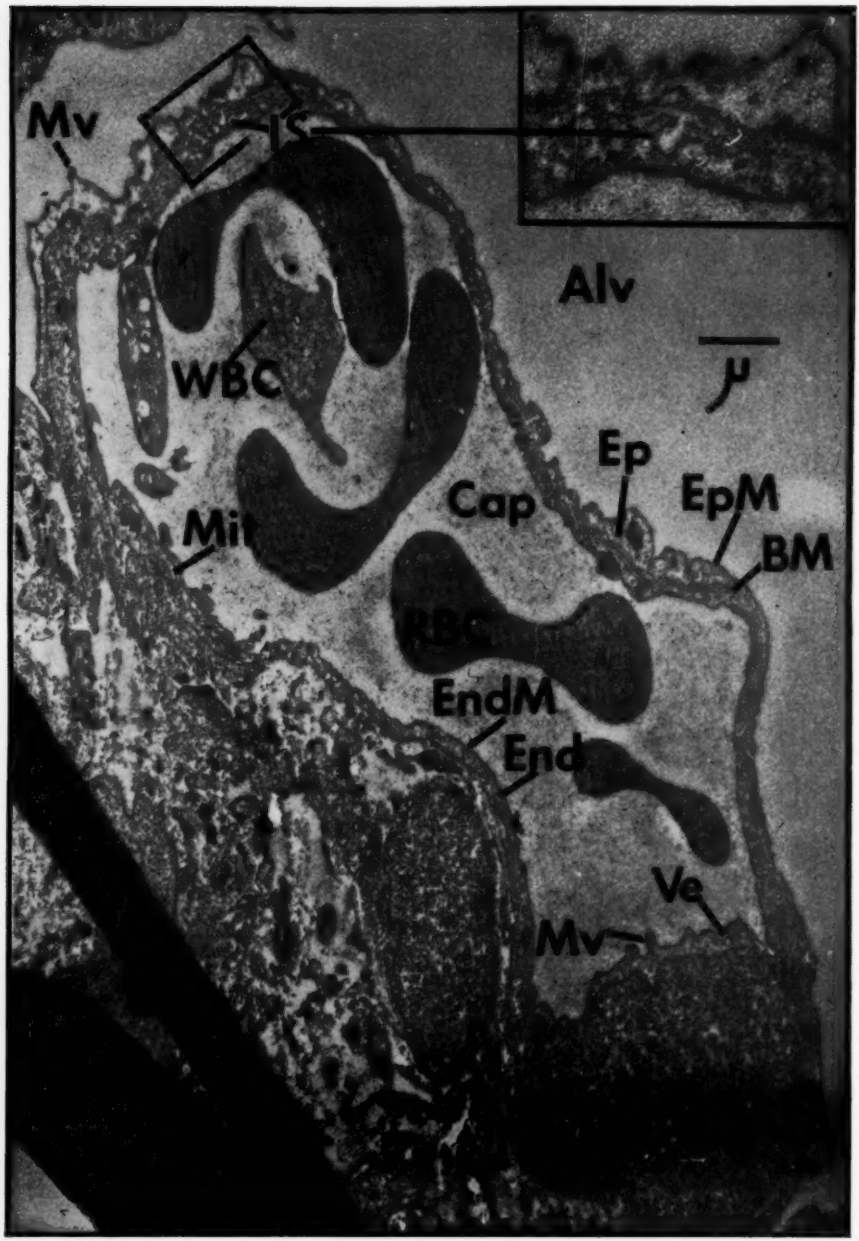

Plate 2
Puppy Lung, x12,000. Insert, x33,000.

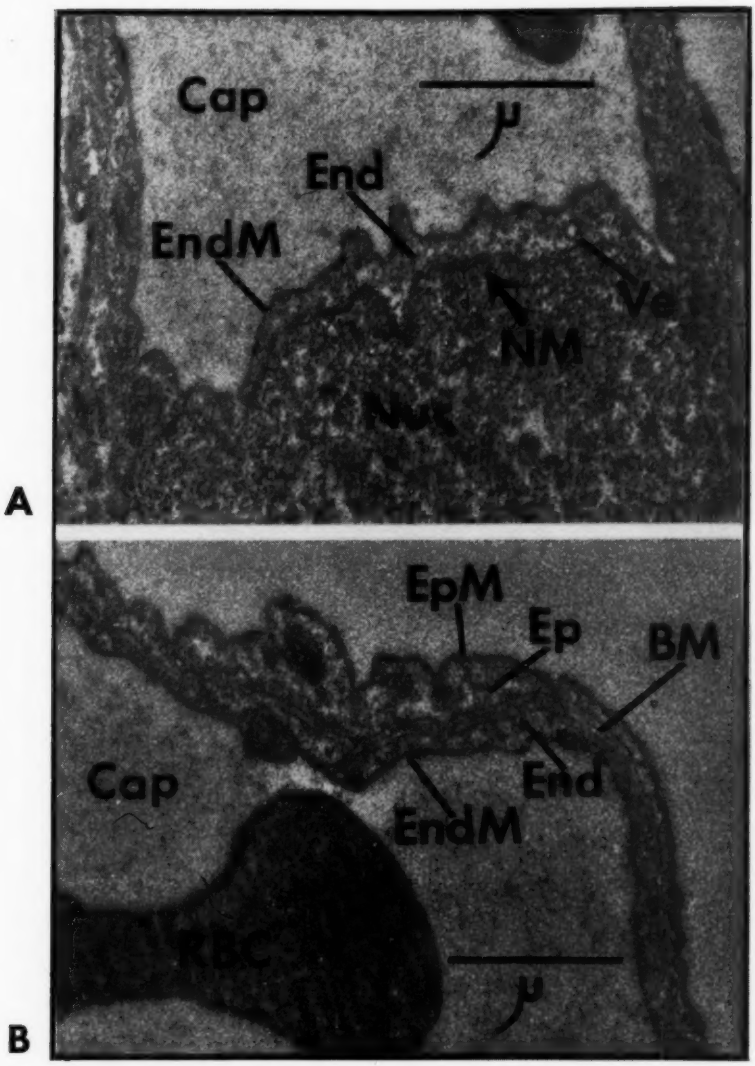

Plate 3

Enlarged Areas of Plate 2, x26,000.

example of a cross section through part of one alveolus and an adjacent capillary. The insert at higher magnifications demonstrates the finer structure of the basement membrane (BM), which in this area demonstrates a *triple* membrane nature. The narrow translucent layer between two thin dense membranes is referred to as the basement membrane. The inner one of these limiting dense areas is presumed to represent the surface membrane of the capillary endothelial cells: the outer one

to represent the inner surface of the alveolar epithelial cells. The third one which is observed in the present investigation is not immediately explainable and has not been reported earlier to our knowledge. Although often detected, plates 1, 3B, 7A, it is not observed continuously in our micrographs but becomes alternately distinct and indistinct along the septum, probably due to variations in the direction of the cut relative to it, or because of local differences in thickness of the section.

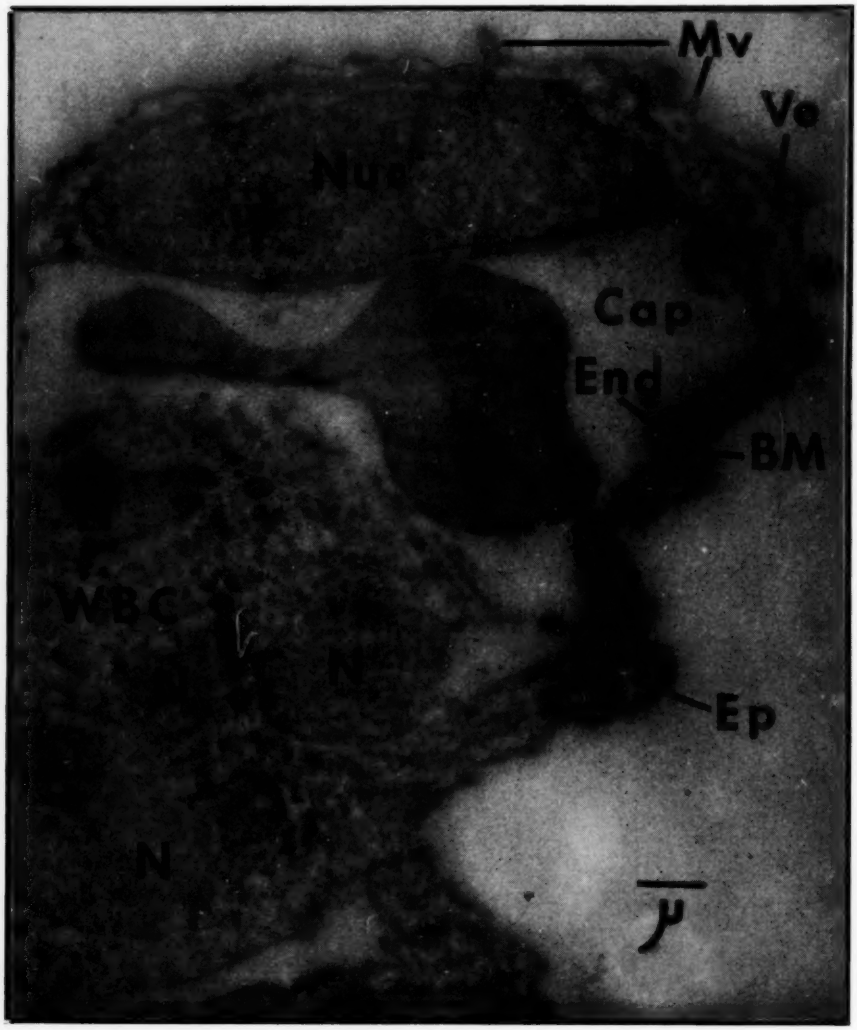

Plate 4
Puppy Lung, x10,000.

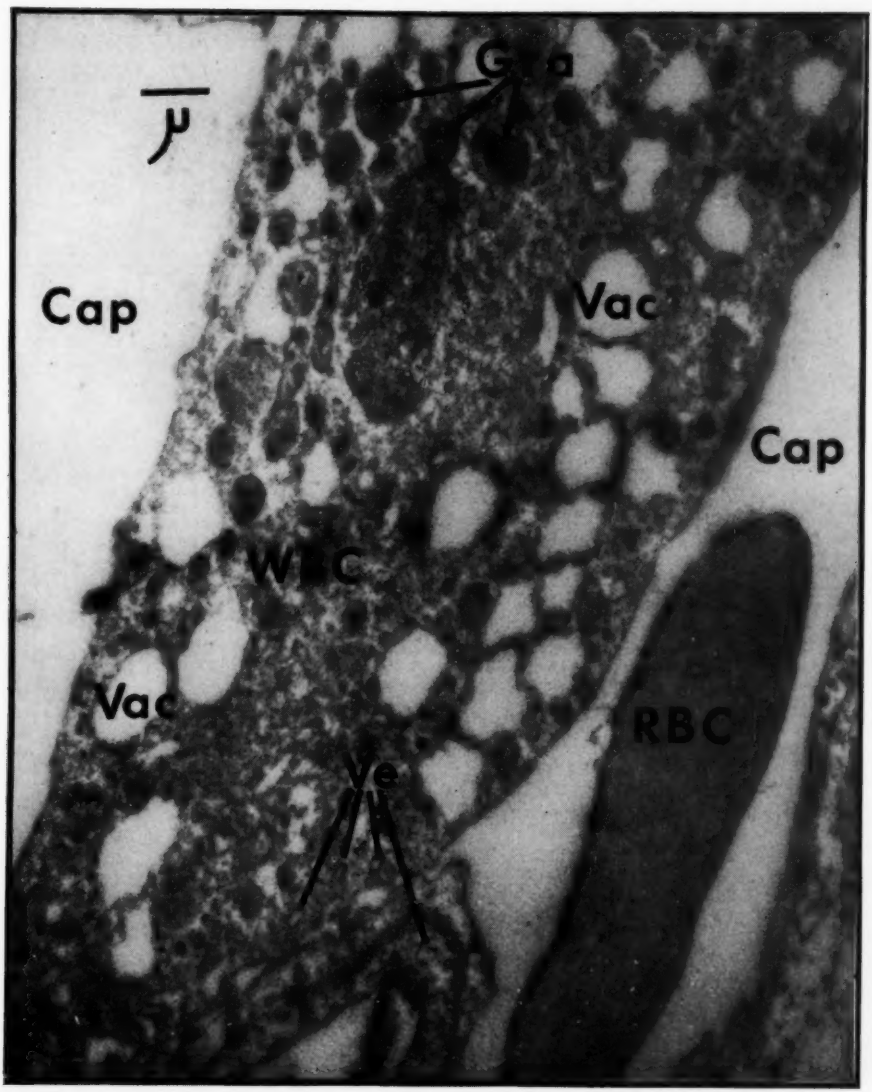

Plate 5

A Leucocyte in a Capillary of Puppy Lung, x10,000.

Immediately facing the alveolus and lining it, is a very thin continuous epithelium (Ep), which has a membrane (EpM) about 100 to 350 A.U* thick, represented in the micrographs as a dark line. The epithelium is composed of a single layer of

*1 angstrom unit (A.U.)=10-8 cms.

Plate 6
Puppy Lung, x20,500.

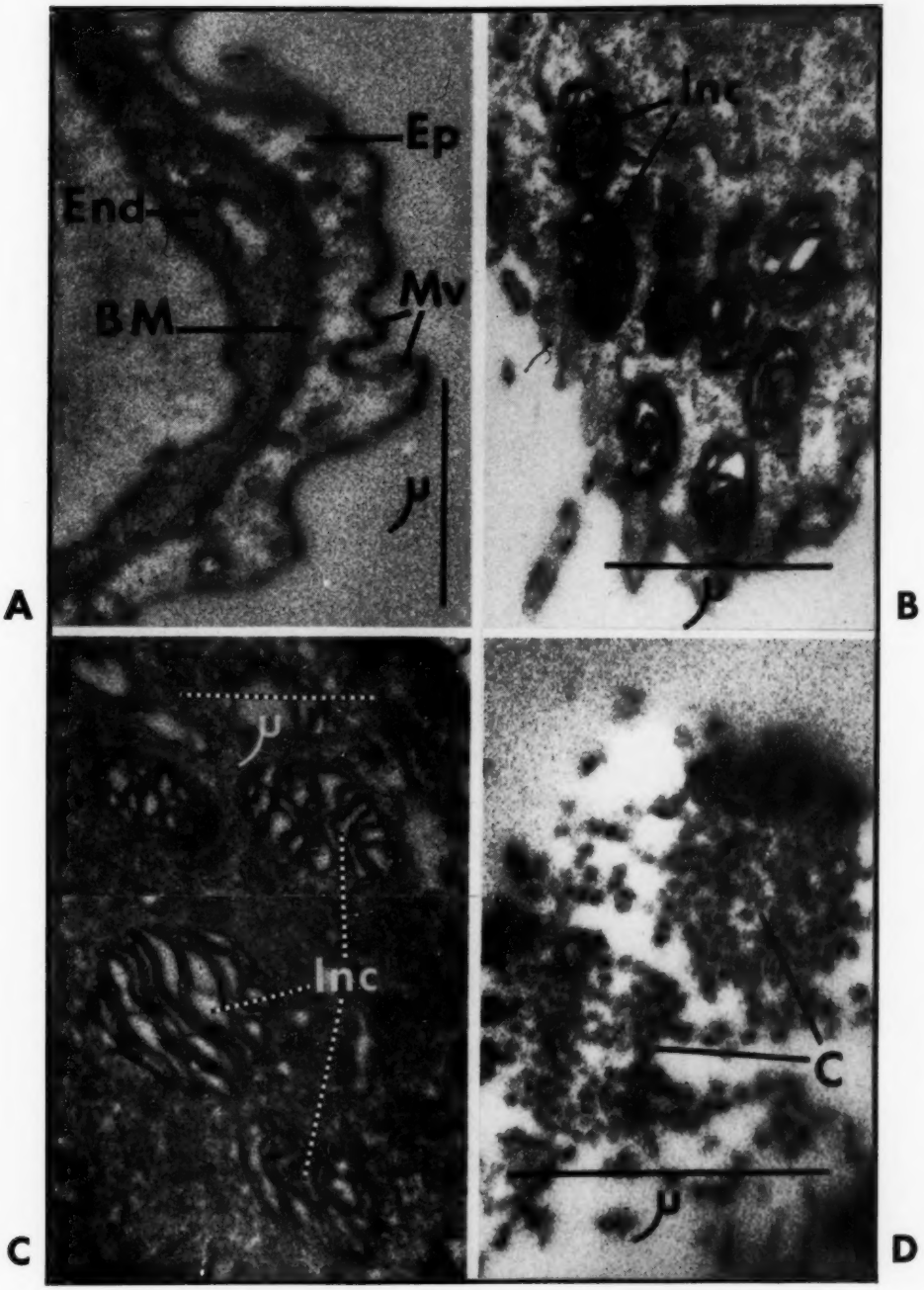

Plate 7

(A) Septum of Puppy Lung, x34,000 (B) Inclusions in Epithelial Cell of Puppy Lung, x34,000
(C) Inclusions in Epithelial Cell of Puppy Lung, x29,000.
(D) Cross Sections of Collagen Fibers in Puppy Lung, x49,000.

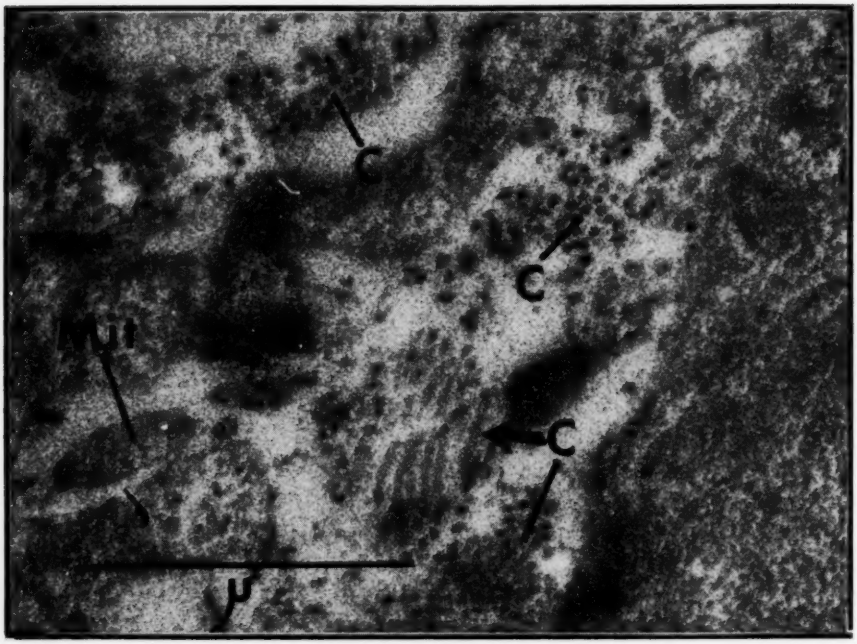

Plate 8

Section of Puppy Lung Showing Occurrences of Collagen, x51,000.

highly attenuated cells and is continuous without interruption in all the fields we have observed. In most cases the width of this epithelial lining is well below the limit of resolution of the light microscope, which is one reason why many investigators at one time doubted its existence[8,9].

We have found that it consists of cells which can attenuate to a thickness as small as about 0.05 μ, or in the region of an epithelial nucleus reach a thickness of as much as 3 μ or more, plate 1. In many places the plasma membrane of the various cell types is seen to project into the capillary or alveolar lumen in short columns or microvilli (Mv), plate 1 and others. Only infrequently was any evidence for the intercellular space (IS) detected in any of our micrographs of the septum, plate 2.

The epithelium lies directly upon the basement membrane. The basement membrane in turn is in direct contact with the capillary endothelium (End). This endothelium is likewise composed of a single layer of highly attenuated cells which surround the capillary lumen. Wherever it widens about an endothelial nucleus (Nuc), the endothelium can be as broad as 3.5 μ or more, plate 2. The endothelial nucleus in plate 3A is bounded by a double nuclear membrane (NM) (at the arrow). Plate 3B shows another enlarged segment of septum wherein the triple structure of the

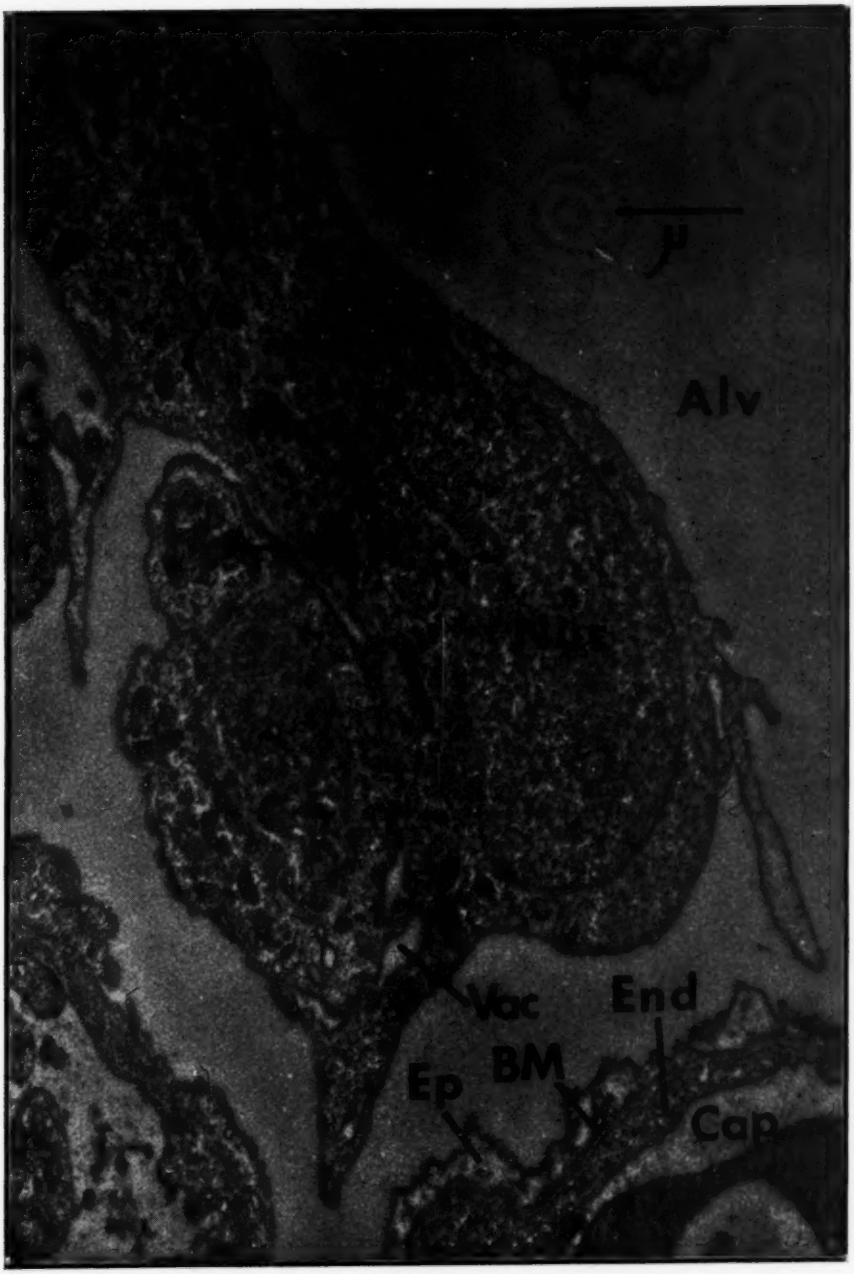

Plate 9

A Macrophage in the Alveolar Space of Puppy Lung, x19,000.

basement membrane is easily observed. The endothelium and epithelium membranes (EndM) (EpM) are also seen.

Within the capillaries, plates 1 and 2, both red and white blood cells (RBC) (WBC) are seen. The red blood cells are smooth in outline and homogeneous. Sometimes the white blood cells, which are more irregular in outline, are cut in such a manner as to demonstrate several segments of a multi-lobed nucleus (N), plate 4. Plate 4 also demonstrates several examples of microvilli (Mv) as well as an endothelial nucleus.

Small rounded profiles, which consist of a thin dark border, or membrane, surrounding a light interior, are observed scattered throughout the cytoplasm of the epithelium and endothelium. These are presumed to be some sort of vesicles (Ve), and are virtually a constant feature of most types of cells, such as the leucocyte in plate 5. Large dense granules (Gra) and large but less dense vacuoles (Vac), have been observed in some leucocytes, plate 5, as well as in certain cells which are probably phagocytic. Also found in the cytoplasm are denser bodies of the same general size, many of which are mitochondria (Mit), plate 6. The ground structure of the cytoplasm of all the cells observed except the red cells, is finely granular. Undoubtedly, some of these granules are the ribonucleic acid-rich granules described by Palade[10]. Again doubled walled nuclei are observed in plate 6 (arrows), and one of the nuclei shows evidence for what may be a nucleolus (Nucl).

Plate 7A shows another example at high magnification of a segment of septum with structure in the basement membrane. There are also several microvilli. Many inclusions (Inc) are also found in the sections. These are composed of closely parallel concentric lamellae, plates 7B and 7C. The inclusions shown in both plates are located in the epithelial cells. Sometimes, as in 7C the structure within these inclusion bodies resembles the cristae of mitochondria, except that the membranes are thicker and denser. This is particularly true in both 7B and 7C where the lamellae in the inclusion bodies are seen to be paired to consist of two dark lines (membranes) separated by a single light line. In different inclusions the lamellae are arranged with a variety of densities, but it may be that their separation is a preparation artifact. There are also evidences in the sections for the endoplasmic reticulum, a closed membrane system described by Porter[11] and Palade and Porter[12].

Although not usually as easily visible with osmium tetroxide fixation alone, as with a combination of staining, what are thought to be collagen fibers were often observed both longitudinally and in cross section, plates 7D and 8. In 7D they are observed in cross section to have a dark outline, with a less dense interior and to have an average diameter of about 350 A.U. The fibers may lie parallel in bundles, or separately without orientation. Plate 8 shows a group of six short fibers (at the arrow), lying parallel to each other in partial longitudinal section, as well as others in cross section.

Plate 9 shows what appears to be an alveolar macrophage. This cell contains a nucleus and several groups of mitochondria as well as large vacuoles and smaller vesicles. It also possesses what would appear to be well developed microvilli.

ABBREVIATIONS

Alv, Alveolus
BM, Basement Membrane
Cap, Capillary
End, Endothelium of Capillary
EndM, Endothelium Membrane
Ep, Epithelium of Alveolus
EpM, Epithelium Membrane
Gra, Granules
Inc, Inclusion
IS, Intercellular Space
Mac, Macrophage
Mit, Mitochondria
Mv, Microvillus
N, Nuclei Segment of Leucocyte
NM, Nuclear Membrane
Nuc, Nucleus
Nucl, Nucleolus
RBC, Red Blood Cell
Ve, Vesicle
Vac, Vacuole
WBC, White Blood Cell
C, Collagen

SUMMARY

Preliminary observations on the fine structure of control puppy lung studied with the electron microscope agree in general with the findings of other investigators who have used this technique with this tissue. A highly attenuated, continuous cellular epithelial and endothelial lining is found to separate the blood capillaries from the air spaces. The basement membrane, which appears to contain a central membrane, previously unreported, is described. A few blood cells are also shown. Cells believed to belong to the macrophage system are discussed. Large, dense, laminated inclusions are found scattered throughout the cytoplasm, and there are occurrences of collagen.

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A METHOD FOR STIMULATION AND SIMULTANEOUS ELECTROENCEPHALOGRAM RECORDING

H. VAN DEN ENDE, E.E. (Delft)*

INTRODUCTION

This report presents aspects of techniques for the recording of electrical activity from one region of the brain, whilst stimulating another region. Recording of electrical activity as well as stimulation is by means of depth electrodes. The work was carried out to develop recording techniques to facilitate the investigation of the Etiology of States of Impaired Consciousness using Rhesus monkeys[1].

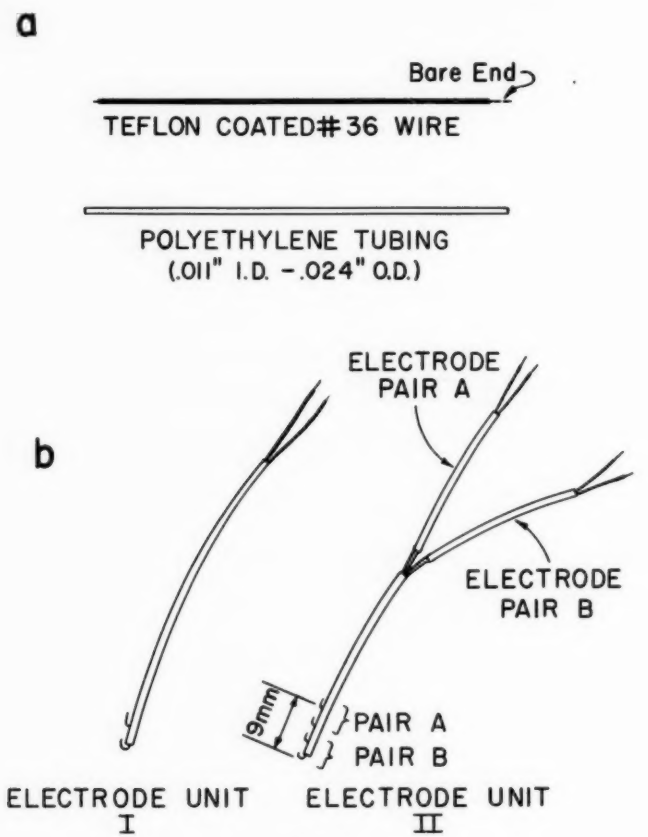

Figure 1
Electrode Units

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ELECTRODE UNITS

Two electrode units were made using teflon coated No. 36 wire, 92% platinum and 8% tungsten. The wire diameter was .005 inch and the teflon coating consisted of three layers each 0.0005 inch thick. Intramedic polyethylene tubing (inside diameter of 0.011 inch and outside diameter 0.024 inch) was used to cover the leads. Parts as sketched in Fig. 1-a being put together to form units as sketched in Fig. 1-b.

For electrode unit I, Fig. 1-b; one incision was made in the polyethylene tubing at 3 mm from the tip, and two wires were threaded through the tubing, one being brought out through the incision and one out at the tip. The teflon coating was then removed for approximately 3 mm by holding the wire ends in a gas flame. After bending the wire tips, the hooks were pulled in place.

For electrode unit II, a similar procedure was followed. Three incisions were now made at 3, 6, and 9 mm respectively from the tip, and four wires were threaded through. The four wires were split up in two pairs.

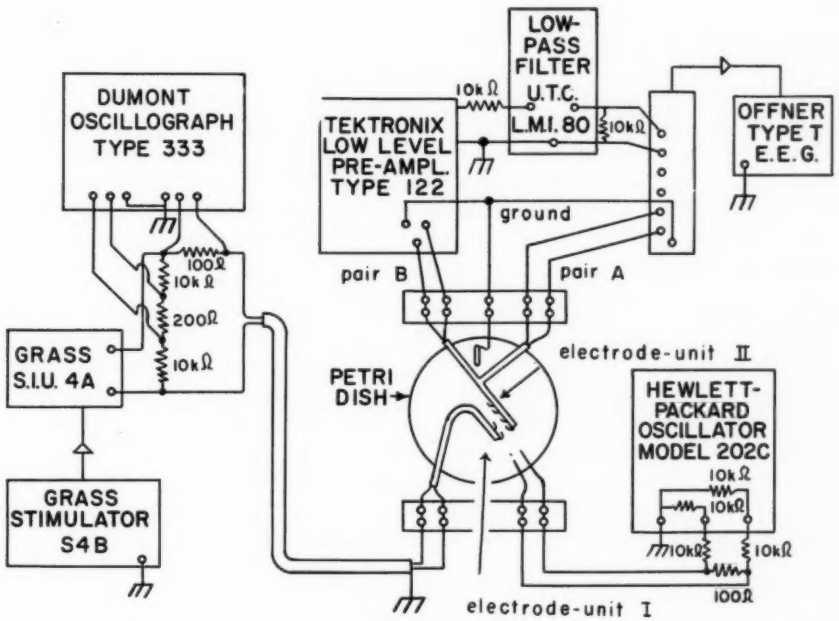

Figure 2

Schematic arrangement of apparatus for the demonstration of recording technique.

ELECTRIC CIRCUITRY

The electrode units I and II in Fig. 1-b were placed in a Petri dish filled with normal saline. They were positioned so that all the hooks (electrodes) were submerged in the saline. The exact location or precise distance of the electrode units was im-

material for this investigation. Two No. 20 wires at an approximate distance of 5 mm were submerged 1 cm and connected to a low frequency oscillator, (Hewlett-Packard, Model 202C). This oscillator simulated brain activity. A set of resistors was provided in order to reduce the voltage to a level suitable for this experiment. The frequency of the oscillator was set to 5 c/s, and the wave shape of the voltage supplied was sinusoidal. The activity set up in the saline was thus far from what would be expected from a monkey brain, but it served a purpose, as will become apparent later.

Electrode unit I is connected via a shielded cable to a combination of stimulator and isolation unit, (Grass Stimulator, Model S4B and Grass Stimulation Isolation Unit, Model 4A). The stimulator can be set to generate a train of rectangular pulses of desired height and width, while the number of pulses per second can be varied over a wide range. The duration of the train in this investigation was 10 seconds. The oscillograph (Dumont, Type 333) monitored the voltage and the current of electrode unit I.

Pair "A" of electrode unit II was directly connected to one channel of the E.E.G. (Offner, Type T) with balanced input. Pair "B" was connected to the balanced input of a battery powered low level preamplifier, (Tektronix low-level pre-amplifier, type 122). The frequency response of this low level preamplifier had a lower half power frequency which was adjustable to one of four values, 0.2, 0.8, 8 and 80 c/s respectively. The upper half power frequency could be set for one of five values, 50, 250, 1,000, 10,000 and 40,000 c/s respectively. The midband gain was either 100 or 1,000 as determined by a 2 position switch. We employed a lower half power frequency 0.2 c/s, an upper half power frequency of 1,000 c/s and a gain of 100, except for the recording of Fig. 7 where an upper half power frequency of 50 c/s was used.

A stainless steel rod submerged in the saline served as animal ground, and was connected to the appropriate terminals of the E.E.G. and the amplifier. The amplifier acted as a generator with an internal resistance of 1,000 Ω. The low pass filter (United Transformer Corporation L.M.I. 80) driven by this amplifier, however, is designed to be driven from a source with an internal resistance of 10 kΩ. For this reason, a 10 kΩ resistance was inserted between amplifier and filter. The filter is designed to be loaded by 10 kΩ and as the input impedance of the E.E.G. was well above this value, a 10 kΩ resistance was provided across the filter output. The frequency response curve of the low-level preamplifier low pass filter combination is shown in Fig. 3. The midband gain of this combination was 50. The filter had a cut off frequency of 80 c/s. The frequency response curve of the low level pre-amplifier with the upper half power frequency set to 50 c/s is partly shown in this figure. The E.E.G. recorder was chopper stabilized, the chopper frequency being 400 c/s.

OBSERVATIONS

The tracings (pen deflections as a function of time) of Fig. 4 were obtained with the set up of Fig. 2. The upper tracing corresponds to pair "A", the lower tracing to pair "B". To the left are calibration pulses, the calibration refers to the

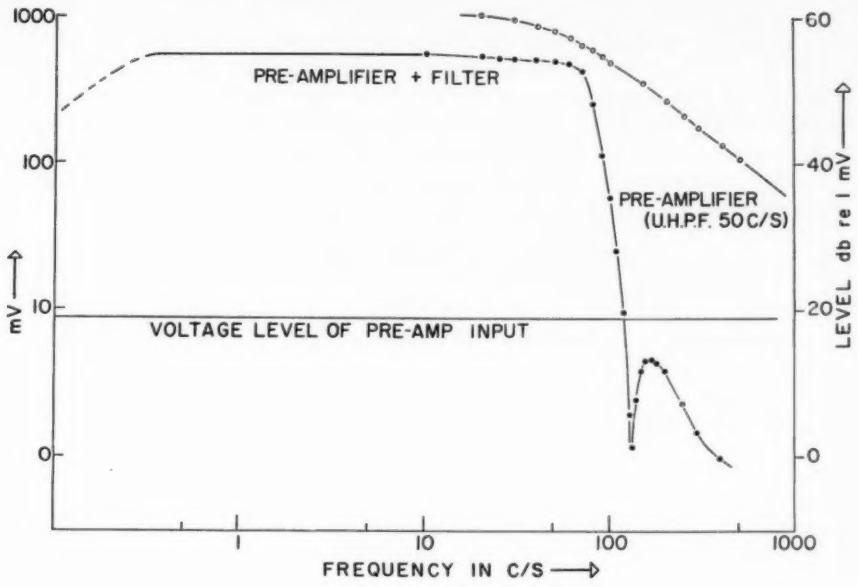

Figure 3

Frequency responses.
Solid circles: Frequency response of low-level preamplifier and filter.
Open circles: Frequency response of low-level preamplifier only, with upper half power frequency set to 50 c/s.

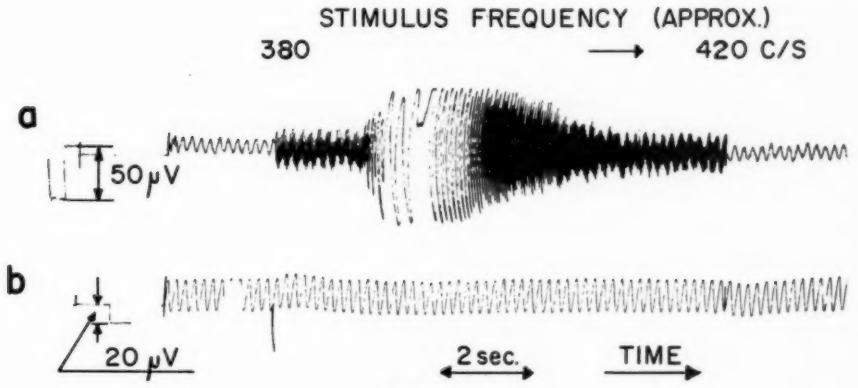

Figure 4

Recordings with arrangement as in Fig. 2. (Stimulating via electrode unit I).
A. From electrode pair A of electrode unit II directly to E.E.G.
B. From electrode pair B of electrode unit II through preamplifier and filter to E.E.G.

input of E.E.G. and low level preamplifier respectively. When switched to recording, the 5 c/s activity stands out clearly and measures peak to peak 14 μV across pair "A" and 40 μV across pair "B". When measuring the 5 c/s activity from one pair

of electrodes (as in Fig. 1) in various positions and locations (in the petri dish), firstly with the low-level preamplifier and secondly with the E.E.G. directly, the voltage as recorded by the former was usually 2 to 3 times the voltage as recorded by the latter. The voltage recorded thus depends on the input impedance of the measuring instrument. The low-level preamplifier input impedance is 20 MΩ paralleled by 50 $\mu\mu$F, while the E.E.G. input impedance is 200 kΩ at 15 c/s. Also noticeable is a noise component on the upper tracing (Fig. 4) which is due to the E.E.G. input stages. This noise component is roughly 2 μV as judged from the record.

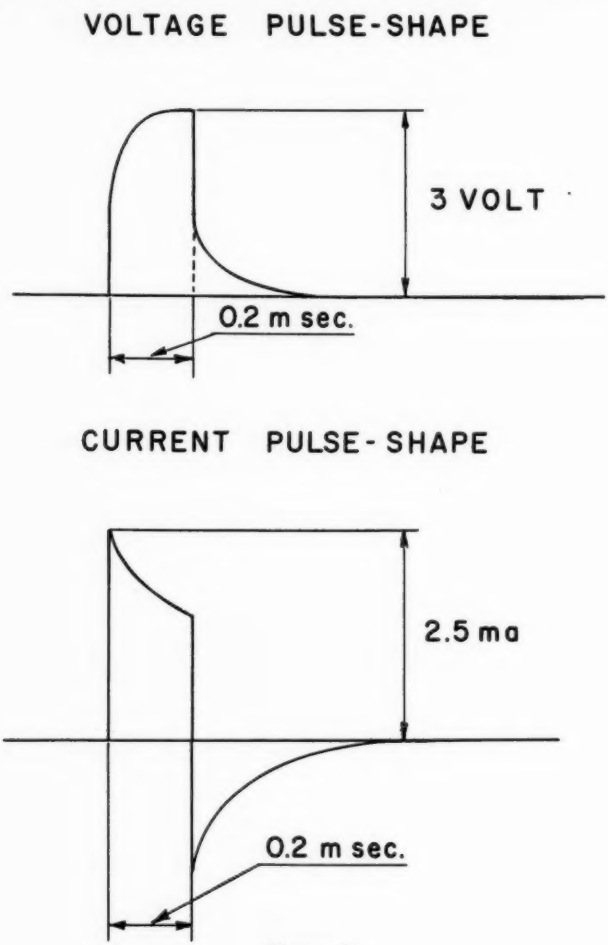

Figure 5
Stimulus voltage and current pulse forms.

A stimulus consisting of a train of pulses (for voltage and current shape and size, see Fig. 5), the repetition frequency of which was gradually varied from 380 to 420 c/s in a 10 second period, was turned on 2 seconds after commencement of

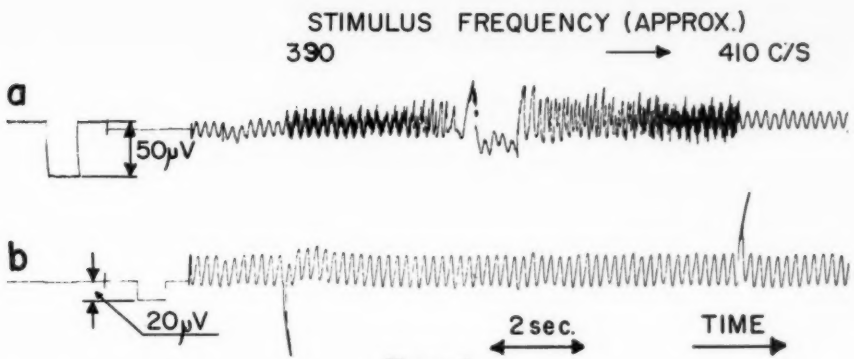

Figure 6

Recordings with similar arrangement as in Fig 2. (Stimulating via pair A of electrode unit II).
A. From electrode unit I., directly to E.E.G.
B. From electrode pair B of electrode unit II., through preamplifier and filter to E.E.G.

recording. This stimulus gives rise to large pen deflections in the upper tracing, the frequency of which seems to be related to the stimulus frequency. The pen frequency decreases from the onset of stimulus, goes through zero about five seconds later and increases subsequently. (The chopper frequency was 400 c/s.) The stimulus onset causes a spike in the lower tracing, but leaves otherwise the recording of slow 5 c/s activity unaffected. Ten seconds later stimulus was turned off causing a spike in the lower tracing. The tracings of Fig. 6 were obtained after the following changes in circuitry. Electrode unit I was connected to the E.E.G., and pair "A" of electrode unit II was connected to the stimulator. Pair "B" remained connected to the low level preamplifier and filter. The stimulus voltage and current pulse shape and size were as in Fig. 5. The upper tracing shows stimulus artefact somewhat smaller than in Fig. 4. The lower tracing has more pronounced spiking when turning the stimulus on and off. Slow activity of 30 μV peak to peak has no stimulus artefact (except for spikes) notwithstanding the fact that the stimulation voltage (see Fig. 5), is approximately 10^5 times larger than the signal recorded. Pair "A" and "B" were 6 mm apart whereas the distance between the two electrode units was approximately 1 cm.

DISCUSSION

The E.E.G. with chopper stabilization is not intended to be used for the recording of electrical activity of the brain whilst stimulating electrically some other area of the brain. For instance, when the stimulus frequency f_s is slightly less than the chopper frequency f_c, $\frac{1}{2} \cdot \frac{f_s}{f_c - f_s}$ pulses in a row will be presented to one contact of the chopper, the next $\frac{1}{2} \frac{f_s}{f_c - f_s}$ to the other contact. This cycle which takes $\frac{f_s}{f_c - f_s} \cdot \frac{1}{f_s} = \frac{1}{f_c - f_s}$ seconds to complete will thereafter repeat itself again and again.

A theoretical investigation by means of Fourier analysis, and assuming that the chopper circuit is followed by an A.C. amplifier with 400 c/s center frequency and with restricted band width, predicts a pen frequency $f_{pen} = 2|f_c - f_s|$, which relation

was verified. This demonstrates sufficiently, that when an E.E.G. with chopper stabilization is to be used in conjunction with stimulation, a means should be provided to turn the pen writers off whilst stimulating.

The low level preamplifier when used on upper half power frequency 50 c/s will amplify stimulus frequencies above 50 c/s to a lesser extent than the brain electrical patterns below 50 c/s. This filtering action is not sufficient to prevent stimulus interference as demonstrated in the lower tracing of Fig. 7 which was obtained whilst recording from pair "B" and stimulating on pair "A". The voltage and current pulse shapes were similar to those used before and the amplitudes were 0.35 volt and 0.35 mA respectively.

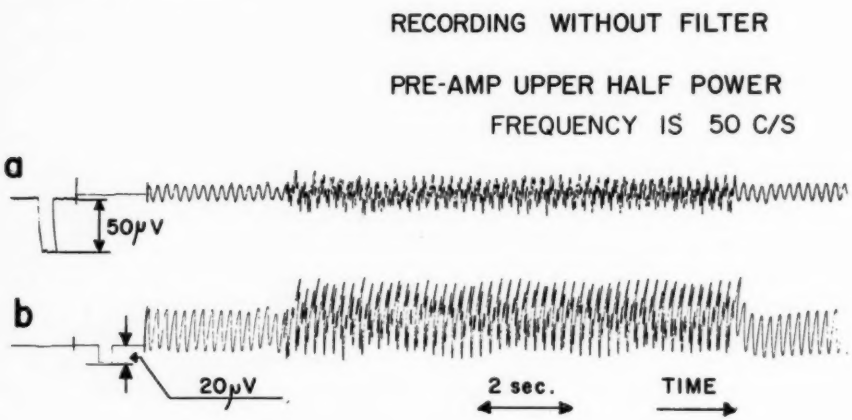

Figure 7

Recordings as in Fig. 6, but after removal of the filter and the adjustment of the upper half power frequency of the low-level preamplifier to 50 c/s. (Stimulating via pair A of electrode unit II).
A. From electrode unit I., directly to E.E.G.
B. From electrode pair B of electrode unit II., through *only* preamplifier to E.E.G.

Using the quadruple electrode unit, described above (as a depth electrode), E.E.G. recordings have been obtained during stimulation areas of the brain of the Macaca mulatta. Figs. 8 and 9 demonstrate the filtering efficiency of the system described above. The technique of placement of this type of depth electrode has been described in a previous publication[1]. The presence of stimulus was monitored by bleeding an appropriate proportion of the stimulating voltage through one E.E.G. channel.

CONCLUSION

A filtering system has been described which makes it possible to record brain activity during electrical stimulation of the brain with pulse repetition frequencies of 130 c/s or higher at a distance as close as 6 mm from the recording electrodes.

The author wishes to thank Dr. L. D. Proctor and J. Lukaszewski for their assistance during this investigation.

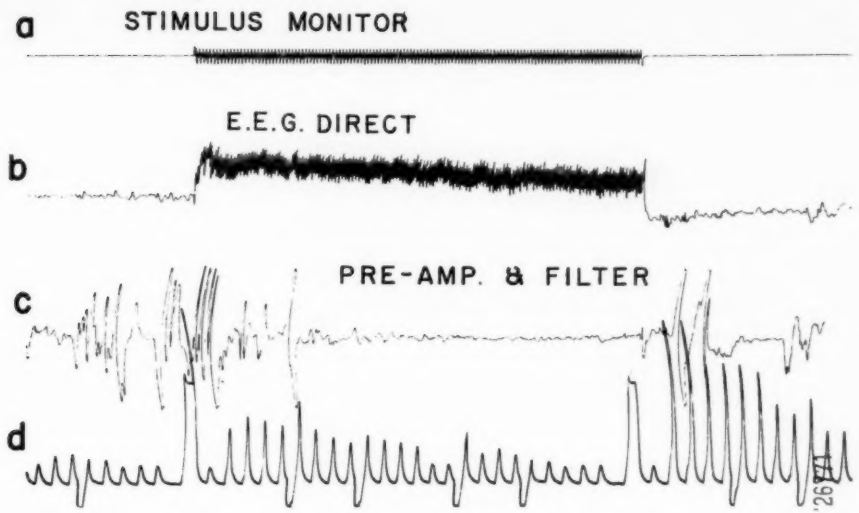

Figure 8

A. Monitor of presence of stimulation applied to a pair of electrodes in the mesencephalic reticular formation of a Macaca mulatta.

B. E.E.G. from a pair of electrodes in the hypothalamus with E.E.G. recorder connected to electrode terminals directly.

C. E.E.G. from a second pair of electrodes at a distance of 6 mm from those in B., using the low-level preamplifier and filter.

D. Record of frequency analysis of E.E.G. in C.

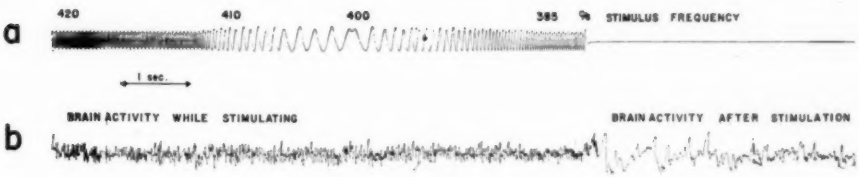

Figure 9

A. Monitor of presence of stimulation applied to a pair of electrodes (3 mm apart) in the hypothalamus of a Macaca mulatta. Note frequency change.

B. E.E.G. from pair of electrodes in the mesencephalic reticular formation, 15 mm from stimulating electrodes, using the low-level preamplifier and filter.

Note the change in brain activity upon cessation of stimulation.

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FRIEDREICH'S ATAXIA AND ITS CARDIAC MANIFESTATIONS

HENRY H. GALE, M.D.*

Associated system disease is a particularly interesting facet of medicine. The association of neurologic disease and cardiovascular disease is well known in syphilis, less known in myotonia atrophica and in progressive muscular dystrophy and relatively unknown in Friedreich's ataxia. This is particularly interesting since Friedreich[1] in his original description in 1863 of six cases described clinical cardiac abnormalities in five.

Friedreich's ataxia is classified among the hereditary ataxias, (Table 1) a group of closely related disorders having a familial basis. They usually breed true but there are occasionally transitional forms. They are characterized by localized degeneration of parts of the nervous system in various combinations and by a slowly progressive course.

Table 1

Hereditary Ataxias (2)

1. Hereditary spastic paraplegia.
2. Hereditary ataxia resembling disseminated sclerosis.
3. Sanger-Brown's ataxia.
4. Friedreich's ataxia.
5. Marie's cerebellar ataxia.
6. Progressive cerebellar degeneration.

These diseases share certain common pathologic features. There is degeneration of ectodermal elements of the nervous system, the nerve fibres are more severely affected than the ganglion cells and the cerebellum and spinal cord are smaller than normal and bear the brunt of the degenerative process. With all these common features clinically and pathologically it is not surprising that differential diagnosis is often difficult. This review is to re-emphasize the importance of the cardiovascular examination and in particular the electrocardiogram as an aid in differential diagnosis.

Friedreich's ataxia is a chronic, progressive, heredo-degenerative disease having its onset usually between 5 and 15 years, though abnormalities such as pes cavus may be discovered in apparently normal members of affected families in early childhood. It is the most common of the hereditary ataxias.

The characteristic pathology[3] of the nervous system reveals degenerative changes especially in the posterior and lateral columns of the spinal cord. These changes are most severe in the lower cord and diminish towards the medulla. The degeneration involves the fasciculus gracilis and cuneatus, the dorsal spinocerebellar tracts, the corticospinal tracts and the cells of Clarke's column. Occasionally the medulla oblongata and cerebellum are involved. The dorsal roots are involved but rarely the anterior horn cells. There is a reactionary gliosis in the degenerated fiber tracts.

The cardinal neurologic symptoms[3] of Friedreich's ataxia include the following. Ataxia is invariably present. It is most marked in the lower limbs. The patient walks

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with a "broad base", tends to stagger and later is unable to walk without support. Romberg's sign is usually positive. A very late sign is upper limb ataxia with an intention tremor. Nystagmus is present in 70 per cent of the cases particularly on lateral gaze. Dysarthric speech is frequently present and may be described as slow, monotonous, unclear, slurred and explosive with scanning and syllabilization. It is frequently accompanied by vigorous grimaces and associated facial movements.

Pyramidal tract degeneration marked clinically by extensor plantar responses, absent abdominal reflexes and weakness of the lower limbs appears. The deep tendon reflexes are usually diminished to absent due to interruption of the reflex on the afferent side. The ankle jerks are lost before the knee jerk. Occasionally the knee jerk may be exaggerated due to a pyramidal lesion even with the ankle jerk decreased. The tone varies from slightly spastic to hypotonic depending on the relative severity of loss of afferent impulse from muscle, tending to diminish muscle tone, and the influence of the pyramidal lesion tending to increase it.

Sensation is inconstantly affected. Position and vibration sense are usually impaired. The sphincters are unaffected. Scoliosis and pes cavus with equinovarus are nearly always present. The scoliosis is due to interruption of afferent impulses from the spinal muscles regulating posture while the pes cavus is due to pyramidal degeneration occurring at an early age with subsequent contractures of the calf muscles. Some authors, however, feel that it is a congenital bony abnormality independent of the nervous system.

Certain ocular manifestations are occasionally seen. They include retinal pigmentation, ptosis, ophthalmoplegia, abnormal pupillary reflexes and rarely optic atrophy. These patients are usually intact mentally although a mild dementia is not uncommon in the later stages of the disease.

The course is usually slowly but steadily progressive although arrested cases are reported. Few live more than twenty years after the onset of symptoms, death being from intercurrent infection or heart failure.

CARDIAC MANIFESTATIONS

The association of a chronic, diffuse, nonspecific myocarditis with Friedreich's ataxia has received scant attention in the English medical literature considering the frequency of their coexistance.

Friedreich[1] in his original description in 1863 described six cases of chronic progressive ataxia of early onset, five of which showed clinical cardiac abnormalities. On post-mortem examination of three cases, two revealed fatty degeneration of the myocardium and one revealed diffuse cardiac hypertrophy with aortic and mitral valvular disease suggesting rheumatic heart disease. Pitt[4] in 1887 emphasized the cardiac manifestations associated with Friedreich's ataxia. Necropsy findings in his case revealed diffuse interstitial myocardial fibrosis.

Loiseau[5] reviewed the literature in 1938 putting forward the theory of degeneration of vagal nuclei resulting in sustained sympathetic hypertonia. In his collected series there were sixteen autopsied cases, six with cardiac hypertrophy, four with dilatation and three with valvular lesions. Fatty degeneration was found in six.

In 1946 Dorothy Russell[6] reviewed four autopsied cases, three of whom had clinically manifested heart failure. Hypertrophy of the heart, diffuse interstitial myocardial fibrosis, and fatty degeneration with normal valves and endocardium was present in all four cases. Two cases revealed atheromatous involvement of the coronary arteries. She proposed the "toxin" theory as the underlying etiologic factor in both cardiac and neurologic manifestations. She did not find any significant changes involving the vagal nuclei.

From the clinical and electrocardiographic viewpoints Evans and Wright[7] in 1942 described thirty-eight cases. Twelve showed definite and significant ECG abnormalities. An additional ten cases revealed minor abnormalities. The more widespread the nervous changes the more heart involvement was present. A positive family history gave more cardiac involvement and affected members of the same family tended to show identical ECG changes.

In 1946 Piron[8] theorized that the cardiac manifestations are caused by lesions of the nervous system. In support of this he presented a case of a twenty-two year old male who had a fatal myocardial infarction after a skiing injury that damaged the dorsal spine. The similarity of the cardiac manifestations and nervous system lesions in this case to those observed with Friedreich's ataxia led him to consider the cardiac involvement in Friedreich's ataxia an additional manifestation of neurologic damage.

More recently Nadas, Alimurung and Sieracki[9] in 1951 described the ECG changes in more detail. They found patterns uniformly showing inverted T waves in the complexes representing left ventricular potentials, that is AVF (in vertical hearts) and V_5 and V_6. Some of the chest leads showed inverted T waves in V_1 through V_4 which can occur normally in children. The inverted T's in V_5 and V_6 are however completely abnormal suggesting ischemia of the left ventricle. On the basis of the now numerous reports of anginal syndrome, autopsy reports of atheromatous involvement of the coronary arteries and now ECG evidence of coronary artery disease, theories [3,9] have been advanced that the coronary artery involvement may play a role in the production of myocardial fibrosis. There is, alas, no explanation of the etiology of this arterial change.

The pathology of the heart and coronary arteries has been inconsistent and has not followed any definite pattern. Grossly there is cardiac hypertrophy involving all chambers but especially the left ventricle. The endocardium and valves are normal while the coronary arteries are highly variable ranging from normal to diffuse atheromatous involvement with or without obstruction. There is seen to be fatty degeneration and diffuse interstitial fibrosis of the myocardium with dilatation. Occasionally pericardial effusion is found with fibrous pericardial thickening and epicardial petechiae and hemorrhage.

Microscopically there is found to be destruction of the cardiac muscle by focal coagulation necrosis of its fibres. There is collagenous tissue replacement of the degenerating myocardium with a compensatory hypertrophy of the remaining uninvolved fibres. The nuclei of the muscle fibres are large, vacuolated and hyperchromatic. The cross-striations are usually absent. There are longitudinal fibrils occupying the peripheral sarcoplasm with a granular cytoplasm in the center of the cell and with lipochrome pigment present. The Purkinje fibres of the node and conducting system are separated by fibrous tissue and a sparse cellular infiltrate, usually lymphocytes and eosinophiles but occasionally mast cells or neutrophilic leukocytes.

Pathologic examination of the remainder of the organs revealed only chronic passive congestion in liver, spleen and lungs with occasional pleural effusions.

It is noteworthy that the cardiac disorder was the presenting complaint in a significant number of patients. Clinically the signs and symptoms varied with the heart size, that is, with the stage of the disease. The common findings were arrhythmias, congestive failure, and anginal syndrome.

Many different arrhythmias have been reported[3] including normal sinus rhythm with numerous atrial or ventricular premature systoles, paroxysmal atrial tachycardia, atrial fibrillation, parasystolic ventricular rhythm, bundle branch block and complete heart block. These are probably due to involvement of the conducting system by fibrosis with disruption of the normal pathways.

The described murmurs were also variable[3,4,9,10] and were heard over the mitral, aortic and pulmonary areas. The murmurs varied in timing being either systolic or diastolic (proto-, mid-, or presystolic). In numerous autopsies there was complete failure to account for these murmurs by organic valvular damage.

Considerable difficulty is often encountered during life in deciding whether there is coexistant rheumatic valvulitis to account for the heart murmurs. Careful search histopathologically has failed to reveal these characteristic changes in all the series reviewed. The murmurs then are probably due to the marked dilatation of the left ventricle relative to the mitral orifice.[10] Further evidence in this regard is that tachycardia often emphasized the murmurs showing the importance of blood velocity in the production of the murmur.

The presence of electrocardiographic abnormalities suggests the eventual onset of heart failure or arrhythmia. Cardiac signs and symptoms can occur in the absence of left ventricular enlargement especially in association with rapid irregular heart action. The addition of cardiac enlargement however worsens the prognosis and heralds further or progressive cardiac failure. The arrhythmias and congestive failure respond for a time to the standard therapeutic measures for their relief.

The etiology remains obscure. Early workers ascribed the myocardial changes to bulbar sclerosis involving the vagal nuclei[5] and thereby facilitating sympathetic

overactivity. Careful review histopathologically has failed to corroborate this theory[6]. Later an unknown toxic agent[6] was held responsible for both the myocardial and the neurological lesions. Fatty degeneration may be caused by toxins or by lack of oxygen. The bacterial toxins are organic poisons, and fatty degeneration is frequently seen in acute and chronic infections. Phosphorous, chloroform and alcohol are the most common inorganic poisons resulting in fatty degeneration. Pernicious and secondary anemias both cause insufficient oxygenation leading to fatty degeneration. Investigation along these lines has failed to unearth any clues etiologically.[3]

The association of abnormal ECG changes and a positive family history with affected members of one family showing the same type of change certainly suggests the inheritance of a lethal gene[11,12] affecting both heart and nervous system. There are no racial, geographic or social factors related to the disease. The primary cause appears to be an inherited abnormality. Since the condition usually appears before the age of puberty, the chance of inheritance beyond a single generation is reduced. The lethal gene may result in true Friedreich's ataxia, Friedreich's ataxia associated with the cardiac disorders, variants of Friedreich's, and intermediate forms of the degenerative processes within the central nervous system. Certain authors have suggested the heart alone may be affected.[12]

Roth[13] reports a family with Friedreich's ataxia in a mother and a daughter and heart disease in five other members of the same family over three generations. The mother with Friedreich's ataxia had six siblings, four of whom had heart disease. Her father died suddenly of heart disease at age 62 and one brother died at 34 of heart disease. The details of the cardiac disorder is unknown in these cases but it does lend support to the concept of a lethal gene responsible for Friedreich's ataxia and familial cardiac disorders.

CONCLUSIONS

Friedreich's ataxia should not be regarded as a disease of the nervous system alone but as a degenerative disease of unknown origin with a predilection for the nervous and cardiovascular systems.

Since it has been estimated[7] that electrocardiographic changes are observed in 30 per cent of patients with Friedreich's ataxia, the electro cardiogram is a diagnostic aid which may help to establish the diagnosis of Friedreich's ataxia when the neurologic manifestations are not altogether typical.[12] While a normal tracing does not exclude diagnosis of this disease, an abnormal record lends valuable support to the diagnosis.[9] Conversely in a young patient showing signs of coronary insufficiency or unexplained cardiac symptoms a complete neurological investigation may establish the diagnosis.[14]

The frequent presence of myocardopathy in Friedreich's ataxia is now well established, although the cause remains obscure. The rarity of its observation may be due to failure to investigate this association. The diagnosis of Friederich's ataxia should demand a thorough evaluation of the cardiac status.

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HYDROCHLOROTHIAZIDE IN THE TREATMENT OF CONGESTIVE HEART FAILURE

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INTRODUCTION:

The past two years has seen the introduction to the medical profession of a new class of potent oral diuretic agents, derived from the aromatic sulfonamides and belonging to a group known as benzothiadiazines. This major break-through in producing a non-toxic and highly active oral diuretic resulted in the development of chlorothiazide, 6-chloro, 7-sulfamyl, 1, 2, 4-benzothiadiazine-1, 1-dioxide.[1] Since then, a second and more powerful derivative, hydrochlorothiazide, has been synthesized and is designated as 6-chloro-7-sulfamyl-3, 4-dihydro-1, 2, 4-benzothiadiazine-1, 1-dioxide. Figure 1.

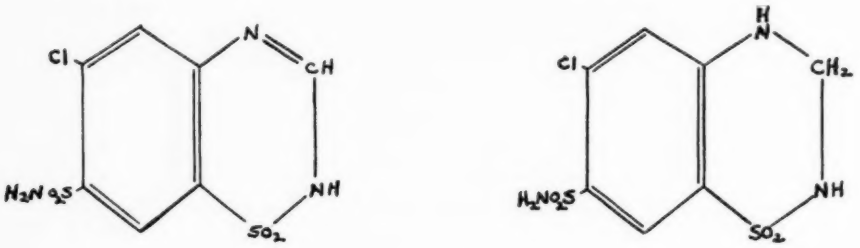

Figure 1

Both compounds are active saluretic agents, causing the excretion of large amounts of sodium, chloride and to a lesser extent, potassium. It is to this activity that they owe their effectiveness in the management of edema states, particularly congestive heart failure.

MODE OF ADMINISTRATION:

The comparable dose to 500 mgms. of chlorothiazide has not been concluded upon by the writers, but would appear to be somewhere between 50 and 100 mgms. The plan was to match 50 mgms. of hydrochlorothiazide to 500 mgms. of chlorothiazide. Some cases appeared to do as well on this program, but others required 150 mgms. of hydrochlorothiazide each day to equal 1,000 mgms. of chlorothiazide. It would appear that if the effects of hydrochlorothiazide are more prolonged,[2] a wider spacing of eight hours between doses might provide longer coverage and better diuretic effects. It also may be continued for long periods of extended therapy, the same as chlorothiazide, but caution must be used to avoid electrolyte depletion effects, as it does appear to depress chlorides more than chlorothiazide.

This drug may be administered intravenously in its lyohydrochlorothiazide form, 50 mgms. being diluted in 5 to 10 cc. of distilled water. This amount comes very close to equalling 2 cc. of mercaptomerin or meralluride in effectiveness.

METHOD OF STUDY:

Thirty-two patients with congestive heart failure were treated with hydrochlorothiazide. Fourteen patients had arteriosclerotic heart disease and fourteen had rheumatic heart disease. Two patients had hypertensive heart disease, and there was one case each of congenital heart disease (probable atrial septal defect) and cor pulmonale.

The subjects were divided into three grades of congestive failure, as follows: Table I

GRADE 1: Patients with mild to moderate degrees of congestive heart failure, manifested usually by dyspnea, moist basilar rales, hepatic congestion and slight edema.

GRADE II: Patients with severe congestive failure, usually with marked edema and/or ascites.

GRADE III: Patients with severe congestive failure who had become resistant or refractive to previously used diuretic agents.

All patients were digitalized and the majority had received prior diuretic therapy, mercurials and/or chlorothiazide. One patient in grade I failure, and one in grade II, had received no previous diuretic. Grade I patients were maintained on 400 to 1,600 mgms. sodium diets as indicated, while those in grades II and III were maintained on the 400 mgms. sodium diet.

TABLE I

ETIOLOGY	GRADE I	GRADE II	GRADE III	TOTAL
ARTERIOSCLEROTIC	4 (1)	7 (2)	3	14
RHEUMATIC	3	10	1 (1)	14
HYPERTENSIVE	1	1	0	2
CONGENITAL	0	1	0	1
COR PULMONALE	0	1	0	1
TOTAL	8	20	4	32

( ) toxic changes

Twenty-four patients were hospitalized and the remaining eight were followed at one to four week intervals in the Out-Patient Department. A daily weight was obtained. Blood counts, urinalyses, BUN and serum electrolyte determinations once or twice weekly were obtained on all hospitalized patients. Clinic patients were checked with less regularity, though several maintained a daily weight chart at home.

RESULTS

GRADE I: Eight cases were classified as having grade I congestive failure, four with arteriosclerotic heart disease, three with rheumatic heart disease and one with hypertensive heart disease. Seven of the patients had been treated with previous diuretic programs, all with good response. When changed to hydrochlorothiazide, six of the seven responded equally well to this agent. One case (Case 1) demonstrated a superior response to a mercurial diuretic.

CASE 1: N.A. was a 71 year old white woman who had been followed in the Out-Patient Department since March 1957 with a diagnosis of rheumatic heart disease, aortic insufficiency and cardiac decompensation. She was maintained on a 1 gram salt diet, gitaligin 0.5 mgms. daily, and intermittent injections of mercurial diuretics.

She was admitted to the hospital on December 14, 1958, because of increasing dyspnea, palpitation and ankle edema of two weeks duration. Weight on admission was 106 pounds, and after four days of bedrest and her prior regime, her weight decreased to 104¼ pounds. Seventy mgms. of lyohydrodiuril was administered at this time with a loss of 1¼ pounds. Four days later an injection of 2 cc. of mercuhydrin resulted in a diuresis of 4¼ pounds. During this four day interval the patient showed no evidence of the delayed response to hydrochlorothiazide mentioned below.

One patient in this group not previously treated with diuretics showed a good response.

No toxicity was noted other than weakness in one case after three days of drug administration. This patient had an acute myocardial infraction and could not be weighed, but daily urinary output indicated a good diuresis and the serum chloride level fell to 84 mEq. This cleared promptly when the drug was discontinued.

GRADE II: There were 20 cases in this group, seven with arteriosclerotic heart disease, ten with rheumatic heart disease, and one case each of congenital heart disease, chronic cor pulmonale, and hypertensive heart disease.

One patient had not had previous treatment with diuretics and showed a good response. Of the remaining 19 cases, all had received previous diuretics with a satisfactory response, though the congestive heart failure was not completely controlled in all cases. Seventeen of the 19 cases showed a good response with a weight loss of one to 27 pounds after hydrochlorothiazide was started, the average being seven pounds. Thus, 18 of the 20 cases had a satisfactory diuretic response. Four patients previously maintained on chlorothiazide as the sole diuretic were felt to have an improved diuresis with hydrochlorothiazide.

CASE 2: A.D., a 73 year old woman with arteriosclerotic heart disease, chronic atrial fibrillation and chronic congestive heart failure was followed in the Out-Patient Department. Her passive congestion was incompletely controlled on a 1 gram salt diet, digitoxin 0.1 mgms. daily, diuril 500 mgms. twice daily three days each week and ammonium chloride. Hydrodiuril 50 mgms. b.i.d. was substituted for the diuril three days each week with a prompt loss of 6½ pounds, and considerable improvement in her hepatomegaly and edema, though still not at a dry weight.

In several cases, a prolonged diuresis with a delayed maximal response was noted, partricularly following intravenous administration. This, to our knowledge, has not previously been reported.

CASE 3: L.D. (Fig. I) a 46 year old white man, was admitted to the hospital on December 31, 1958. For two years prior to admission he had increasing dyspnea on exertion, cyanosis, ascites and pedal edema. There was a life-long history of bronchial asthma. Previous treatment included a low salt diet, digitalis and intermittent injections of mercurial diuretics.

Cardiac catheterization showed no evidence of a shunt. Diagnoses of chronic cor pulmonale, obstructive emphysema and congestive heart failure were made.

The patient was continued on digitoxin and a 1 gram salt diet. During the first week he diuresed 14 pounds with bedrest and two injections of mercaptomerin. On January 8, 1959, the patient weighed 202-¾ pounds, and was given 50 mgms. of lyohydrochlorothiazide intravenously. The following morning he weighed 200¼ pounds, and on the day following — 192½ pounds. The same intravenous dose was repeated, and over the next four day period, he diuresed an additional 13 pounds.

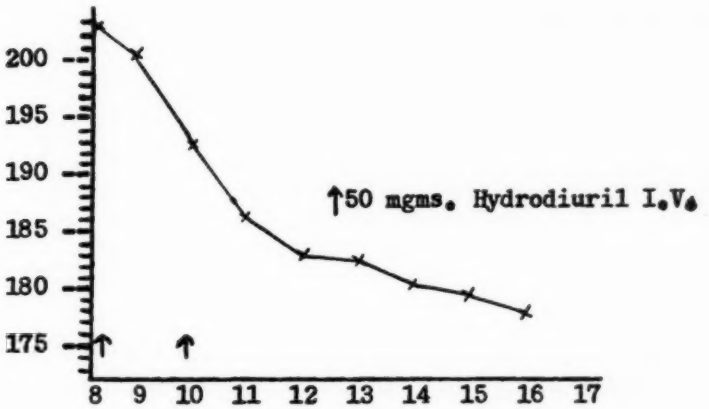

FIGURE I

Two patients in this group responded poorly to hydrochlorothiazide in a dose of 100 mgms. daily. A larger dose might have proven effective, though in our experience some effect can usually be obtained at this dosage level if the patient will respond at all to the drug.

Nausea and weakness occurred in one patient of this group who asked that the drug be discontinued. Serum electrolytes in this case were normal. Weakness and anorexia were noted by a second patient, but drug withdrawal was not necessary. Mild to moderate degrees of hypochloremia were not uncommon, but caused no untoward effects. No cases of hyponatremia or hypokalemia were noted in this series, but these complications have been observed by the authors since preparation of this report.

GRADE III: Four cases of severe, resistant congestive heart failure were given a trial of hydrochlorothiazide. Three were cases of advanced arteriosclerotic heart

disease and there was one case of rheumatic heart disease. All had developed refractoriness to mercurial diuretics and diuril, and showed no response to hydrochlorothiazide. Two patients subsequently showed some response to mercurial diuretics when started on large doses of triamcinolone.

No toxic effects directly attributable to hydrochlorothiazide were noted in these seriously ill patients. One case developed paroxysmal ventricular tachycardia twelve hours after receiving 50 mgms. of hydrodiuril intravenously. This converted readily during the administration of 40 mEq. of potassium in 500 cc. of 5% glucose in water. There were no other signs of possible digitalis toxicity while the serum electrolytes determined at the time showed only a mild hyponatremia (Na 127 mEq.). The relation to hydrochlorothiazide is conjectural.

COMMENT:

Hydrochlorothiazide, like chlorothiazide, causes a marked excretion of sodium, chloride and potassium in the urine, apparently due to a renal tubular blocking action on the reabsorption of these ions. Studies by Moyer and co-workers[4] suggest that the primary action is on chloride excretion in contrast to chlorothiazide, which produces a relatively greater loss of sodium. The two drugs appear to cause approximately equal excretion of potassium. The saluretic effects are greater and more prolonged in the case of hydrochlorothiazide at a comparable oral dose.[3] The latter effect was noted over a protracted period in one of the cases in this report (Case 3). Diuresis is apparently improved when acid salts, potassium chloride and/or ammonium chloride were used as adjunctive therapy in this series. It was somewhat less effective when serum chlorides were at slightly depressed levels and much less effective at moderately depressed levels, i.e. when serum chlorides were depressed after intensive or prolonged therapy below 97 mEq.

Hydrochlorothiazide is well tolerated orally and almost devoid of gastrointestinal side effects, even in the most advanced cases of congestive heart failure with severe visceral congestion. Like chlorothiazide, it remains consistently effective without evidence of drug tolerance and subsequent need of increasing dosage. Approximately two percent of our cases treated with chlorothiazide have developed a mild erythematous skin rash, while none were encountered in this series treated with hydrochlorothiazide. No adequate opportunity has been afforded to test the latter drug in a patient sensitive to chlorothiazide. Hydrochlorothiazide has not produced any toxic renal disturbance since it use was begun. Jaundice has not been reported to date, though this is a rare toxic complication with the use of chlorothiazide.

The greatest danger and toxic effect appears to be severe electrolyte depletion. Mild hypochloremia is a natural consequence of the use of either of these two agents, but if large doses are given over too long a period in salt depleted patients, severe hypochloremic alkalosis, "salt depletion syndrome", and severe hypokalemic effects may be produced. The adjunctive use of potassium chloride orally, and/or ammonium chloride can prevent severe hypokalemia, or hypochloremia, and in our opinion, should be used where heavy dosage of both drugs are employed, particularly over long periods. If severe liver impairment is present, as is so often the case in

long-standing congestive heart failure, loss of potassium may already have occurred, and will be aggravated by this type of diuretic therapy. The depletion of potassium will lead to augmented digitalis effects with typical manifestations of digitalis intoxication, mild to severe, manifested often by unusual digitalis arrhythmias. The authors suspect one of the cases in this report was due to this effect.

It is recommended that regular serum electrolyte determinations be obtained where prolonged administration is used in advanced chronic congestive heart failure, particularly where hepatic or renal disease may be suspected, or known to exist, and to "spot check" others at the slightest suspicion of electrolyte depletion. The latter should be suspected if sudden oliguria, or failure to respond, occurs.

Hypochloremic alkalosis usually responds promptly to the use of ammonium chloride, and may be hastened by the combined use of a carbonic anhydrase inhibiting agent for several days.

Hydrochlorothiazide represents another significant advance in the diuretic management of congestive heart failure, and like chlorothiazide, approaches the effectiveness of parenterally administered mercurials.

SUMMARY:

Hydrochlorothiazide was administered to a series of thirty-two patients with congestive heart failure. It was a potent diuretic for the short or long term management of these cases, and can be administered by the oral or intravenous routes. Dosage and toxicity is discussed.

Drug material for this study was supplied by Merck Sharpe and Dohme, Research Laboratories, Division of Merck and Co., Inc., Philadelphia, Pennsylvania.

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ANALBUMINEMIA WITH THE NEPHROTIC SYNDROME

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INTRODUCTION

Extreme hypoalbuminemia was described as far back as 1924, when Kollert[1] studied a patient with "chronic nephrosis" whose serum albumen was less than one gram. More recently, Hardwicke and Squire in 1955[2] described a 37 year old white female with the nephrotic syndrome whose serum albumin was 1.8 grams and a 14 year old white female whose serum albumin was 1.6 grams. Gitlin and Janeway[3] also in 1955 studied three children with the full-blown nephrotic syndrome whose serum albumin was 0.58 grams, 0.40 grams and 0.61 grams respectively. In 1957, Rytand[4] in commenting on the polycyclic nephrotic syndrome mentioned a 52 year old white male with recurrent edema and anasarca whose serum albumin was 1.8 grams.

One other case of analbuminemia has been reported in the literature Bennold[5] reported the absence of serum albumin in a woman with edema and menstrual irregularities at Tuebingen, Germany in 1954. One other case of analbuminimia (serum electrophoresis) in a 55 year old white male with generalized anasarca, pleural effusions and thrombophlebitis has been studied at this hospital.[6] This patient, unfortunately, was lost to followup in December 1957.

CASE REPORT

A 46 year old white housewife was first seen in June 1957, complaining of a productive cough, dyspnea on slight exertion and pronounced ankle edema. The patient dated her symptoms back to age 21 when she first knew of bronchiectasis associated with frequent upper respiratory infections. Seven years later, during her first pregnancy the patient developed dyspnea and ankle edema and heart disease was suspected. In the subsequent 5 years the patient developed more dyspnea and ankle edema during her pregnancies and during the menses.

In January of 1957 the patient was admitted to another hospital for the treatment of pneumonia. During the course of hospitalization bronchiectasis was found in seven pulmonary segments. At this time, however, congestive heart failure was thought to be present and surgery was indefinitely postponed. After a good response to digitalis and diuretics, the patient was discharged the latter part of January.

Approximately 3 months later the patient was re-admitted because of progressive ankle edema. Proteinuria (1 plus) was present. The patient responded well to diuretics. After a four pound weight loss in four days and less noticeable edema there was no further diuresis with mercurials. Two weeks after admission a four plus albuminuria was found. The albuminuria persisted for about 11 days. The

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possibility of a salt losing nephritis was considered but there was no response to hypertonic saline solution.

The non-protein nitrogen on admission was 40 mg. % and gradually rose to 95 mg. % over the six week period of hospitalization. The lack of response of the patient to diuretics posed the question of electrolyte imbalance. The electrolytes, however, were close to normal values (sodium — 130 MEQ, potassium 5.1 MEQ., CO_2 25.4 MEQ., Chloride 90 MEQ.) The serum proteins were measured during the third week of hospitalization and a marked hypoporteinemia was found (total protein 4.7 Gm. %, albumin 0.9 Grm. %, globulin 3.8 Gm. %). Liver function tests were completely normal except for a serum cholesterol of 970 mg. % with 60% esterified. Considering the possibility of amyloidosis, a Congo red test was done and found to be normal. Kidney biopsy was done for further verification and again no

Figure 1
Needle Punch Biopsy.

amyloid was found. (Fig. 1) The biopsy was not adequate for glomerular changes but mild interstitial nephritis was reported. An intravenous pyelogram showed poor renal function but no structural abnormality was present.

A course of ACTH was started approximately 4 weeks after admission according to the following schedule: 25 U. ACTH i.v. slowly over 8 hours for 3 days, 50 U. ACTH gel i.m. for 5 days, followed by a good eosinophil response but no definite diuresis. Within 48 hours there was subjective improvement in the patient and some degree of drop in the proteinuria. The azotemia showed improvement in that the NPN dropped to 55. Eight days after the corticosteroid therapy was given the patient was transferred to the Henry Ford Hospital on June 6, 1957.

On admission the physical examination showed an emaciated 46 year old white female with evidence of anasarca and avitaminosis. The thyroid was small. There was no lymphadenopathy. Dullness was present over the right base and bronchial breathing was present. Inspiratory rales were present over both bases. The heart was not enlarged. The heart tones were of good quality. No murmurs were present. The apical rate was 25/4 and blood pressure was 110/75. The liver was percussed 2 centimeters below the right costal margin and a fluid wave was present. A four plus ankle edema was present with 3 plus pretibial edema and 3 plus sacral edema. The abdominal wall contained subcutaneous edema.

The hemoglobin concentration was 13.4 gm/100 ml. The white blood count was 21,950, with 82% polymorphonuclear leucocytes, 7% lymphocytes, 5% eosinophils, 2% basophils, 4% monocytes. The platelets were slightly increased. The red cells were normocytic. The urine was weakly acidic (pH 6, pH 5), specific gravity 1.016, 4 plus albumen, contained many hyaline casts with waxy lipoids, without red blood cells. The LE cell preparation was negative. The anti-streptolysin titer was 12 units per cc. Blood chemistries were: Fasting blood 94 mg %, NPN 72 mg. %, total lipids 2070 mg. %, calcium 5.3 mg. %, phosphorus 11.6 mg. %. The kidney function was decreased markedly as the phenolsulfonphthalein was found only in trace amount. The urea clearance, standard, was 14 ml.

Chest fluoroscopy showed a honeycomb pattern in each base suggesting bilateral lower lobe bronchiectasis. The heart was small and pulsation was adequate to exclude constrictive pericarditis. The diaphragmatic excursions were adequate. Electrocardiogram showed small complexes and inverted T waves in all leads.

During the next twelve days the edema remained unchanged and weight showed no downward trend. Retrograde pyelograms were negative. On June 18, 1957, the patient was given two units of salt-free albumin after a 24 hour urine was collected for albumin and the blood taken for an electrophoretic pattern. The electrophoretic patterns of the blood and urine are illustrated in Fig. 2.*

The forty-eight hours following the albumin administration a weight drop from 127 to 124 pounds was noted. The NPN rose to 80 mg. %. On June 26, 1957, the

*Immuno-chemical determination of serum at Detroit Cancer Institute showed 0.628 mcg. of albumen.

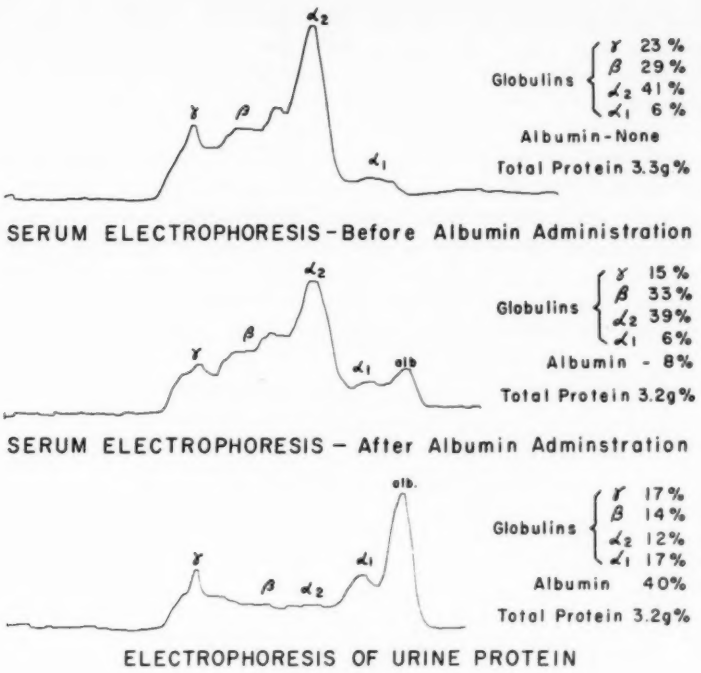

Figure 2

patient was again started on aqueous ACTH (75 U.) without any noticeable effect. One month after admission the patient became extremely restless and then quickly expired. Autopsy permission was not granted.

DISCUSSION

This patient showed all the clinical features of hypoproteinemia, advanced renal disease and bronchiectasis. This case illustrates the complete depletion of the body pool of serum albumen.

In its steady state the rate of synthesis of any constituent in the body pool must equal the rate of dissipation or utilization. In other words, the total body pool of serum protein in its state of dynamic equilibrium is dependent upon its volume, its concentration and the rate at which the input, output and interconversion of the individual components occur.[7]

The total exchangeable pool is equal to the total amount of substance in the body which is available for exchange with additional or newly synthesized molecules of that specific protein.[3] Citrin et al., by tagging albumin molecules with 1131 found that the total albumin pool was 360 Gms. with a daily turnover of about 17.7 Gms. per day.[8]

On the other hand, the turnover time of albumin is the amount of time required for half of the body pool of that protein to be lost. In normal adults the turnover time for albumin is about 11 days.[9] This reduction in the body pool is a stimulus for the hepatic cells to synthesize more albumen.[10]

Kerr, Hurwitz and Whipple presented the first experimental evidence that diet influenced favorably the regeneration of depleted plasma protein. Beef serum was found to favor production of three times as much plasma protein by the hepatic cells as beef heart and more than five times that of beef stomach after plasmaphoresis of dogs to 4 grams of plasma protein. On the other hand, they noted a definite lag in regeneration of serum protein of Eck fistula dogs following acute plasma depletion. Thus, the liver was singled out as the main synthesizing compartment.[11]

As to the increased rate of catabolism in the nephrotic syndrome, albuminuria seems to be of greater magnitude than synthesis of the protein molecule. The exact mechanism of proteinuria in this syndrome is controversial. Hasson and Berkman,[12] emphasize that the tubular reabsorptive mechanism was of greater importance than the glomerular factor. They stressed the tubular atrophy and interstitial atrophy seen in nephrotics secondary to renal vein thrombosis as the most probable lesion responsible for impaired reabsorption. Contrary, to this Chinard,[13] postulated increased glomerular permeability due to increased glomerular capillary pressure and Allen,[14] attributed the changes in the glomerular basement membrane as the responsible lesion in the extensive proteinuria seen the nephrotic syndrome.

The electrolyte disturbance associated with increased renal vein pressure points strongly to the tubules as a major source of dysfunction. Using inflatable balloons Farber, et al.[15] produced elevated pressures at various levels of the inferior vena cava and found a depression of salt and water excretion whether the balloon was above or below the renal vein. Sirota and Nabotoff,[16] postulated a specific tubular effect of venous congestion to account for the depressed salt and water excretion after salt loading on a unilateral renal vein hypertension secondary to a spleno-renal vein anastomosis. Blake and his associates,[17] found that after raising the pressure in the left renal vein for 20 to 30 minutes by means of a clamp in dogs, the water and sodium excretion was depressed but glomerular filtration rate and renal plasma flow remained constant. Talbott,[18] postulated that the loss of oncotic materials from the vascular system leads to a hypovolemic state. This in turn stimulates the neuro-hypophyseal system to retain water and the adrenal to secrete more aldosterone to conserve sodium at the tubular level.

Kark in 1956,[19] reported five patients ranging from 15 to 82 with a gradual onset of edema. All had massive proteinuria, hypoalbuminemia, hypercholesterolemia, casts and oval bodies in the urine. Renal biopsy specimens showed severe tubular degeneration with much interstitial edema. Absence of changes in the glomerular basement membrane contrasted with the findings of autopsy studies of adults dying with the nephrotic syndrome. Kark compares these cases to lipoid nephrosis in children, Kaplan et al.,[20] reported dilated renal tubules with alteration in the tubular

epithelium on renal biopsy in patients with the nephrotic syndrome. Paper chromatography showed increased amino-aciduria.

The case which is presented suggests a tubular basis for the excessive proteinuria, viz. loss of concentrating power in face of low intake, acidosis in the face of alkaline urines, low urinary sodium output in the face of edema.

Since this patient presented an overwhelming hyperlipemia comment should be made on the relationship between this state and the disturbed protein metabolism in this patient.

Four fractions, free cholesterol, cholesterol esters, phospholipids, and the neutral fats comprise the serum lipids.[21] Boyd,[22] in 1937 and Ahrens in 1947, [23] found that the clear sera found in some cases of hyperlipemia was due to the phospholipids' strong surface action preventing coalescence to visible sized particles, whereas neutral fats made up a large portion of the lipemic sera.

Corazzo[24] describes essential hyperlipemia as a clinical state due to the increase in the neutral fat fraction of the blood lipids. He cites the experimental work of Thannhauser and Stanley with I131 labeled fat in which a defective fat clearing mechanism was present.

In contradistinction, alimentary hyperlipemia is a physiologic state in which the neutral fats are normally increased 4-6 hours post-prandially without a rise in the phospholipid fraction. Secondary hyperlipemia is associated with diabetes mellitus, the nephrotic stage of chronic glomerulonephritis, pancreatitis, myxedema, starvation, Nieman-Pick's disease and various lipoidoses, amyloidosis, renal vein thrombosis, the toxic hepatoses and the so-called "pericholangiolitic" hepatitis.

Leiter in 1931,[25] writing on the "lipoid nephrosis" pointed out a disturbed humoral clearing mechanism for the hyperlipemia rather than a disturbance in the actual oxidation and combustion of fat.

It is now generally agreed that essentially all of the cholesterol and phospholipid in human plasma is associated with polypeptides in lipid peptide complexes classified as lipoproteins (alpha or beta). The hypercholesterolemia in adults with the nephrotic syndrome is due to an increase in the plasma concentration of low density lipoproteins (sf 200-300),[26] in association with a decrease in the conversion of the low density lipoprotein to a lipoprotein of a greater density (sf 3-9). This has been attributed to either an increased concentration of the plasma with the low density lipoproteins so that there is a saturation of the normal conversion system, or there is a depression in one or more factors necessary for the conversion or clearing process.[27]

In the transfer of lipid from the blood to the tissue the lipolytic reaction acts as a transport mechanism. In this way the blood stream is cleared of lipid fractions. (Fig. 3) The triglyceride substrate (chylomicra, lipoproteins, artificial oil emulsion)

combines with the fatty acid acceptor, which is the serum albumin and calcium and is transported to the tissue depots as a fatty acid acceptor complex with the formation of glycerol as a by-product.[28] Lipoprotein lipase which is abundant in cardiac muscle and presumably activated by heparin has an enzymatic role in this hydrolysis. As such, an absence of albumin or a deficiency of lipoprotein lipase causes a decrease in the hydrolysis and a defective clearing of hyperlipemia.[29]

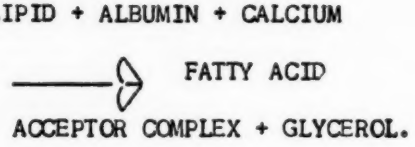

Figure 3

SUMMARY

1. A patient with the nephrotic syndrome is presented with a complete absence of serum albumin.

2. The literature is reviewed on the mechanism of proteinuria. The evidence for suggesting a tubular source of proteinuria in our case was advanced.

3. Hyperlipemia and its basis for existence in the nephrotic syndrome was discussed.

4. A plausible explanation has been offered for the observed clearing of the serum cholesterol which follows repeated infusions of serum albumin.

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THE RELATIONSHIP OF ACETYLCHOLINESTERASE IN THE COCHLEA TO THE OLIVOCOCHLEAR BUNDLE

JOHN A. CHURCHILL, M.D.,* AND HAROLD F. SCHUKNECHT, M.D.**

In a previous publication[1] we demonstrated that AChE was present in the nerve fibers of the cat cochlea; and our original work has been confirmed just recently.[2] Koelle's method[3,4,5] for the histochemical detection of AChE was employed. Briefly, this method consists in incubating tissue specimens in a solution of acetylthiocholine in the presence of cupric ion. Thiocholine liberated by enzymatic hydrolysis is percipitated in the tissue as copper thiocholine. This substance is converted to copper sulfide when placed in ammonium sulfide. Thus copper sulfide, a stable precipitate, is seen where AChE had been active.

The method was applied to cochleas in a special manner. The stapes were removed from the oval windows and the round window membranes were punctured. Polyethelene tubes were cemented in the round windows; and the cochleas were perfused with the reagents. After treatment the cochleas were perfused with formalin, decalcified in trichloracetic acid, sectioned and counterstained.

We thought that the dense staining from AChE seen in the cochleas might be related to the efferent nerve fibers of Rasmussen's olivocochlear tract, rather than to the hair cells or dendritic endings of spiral ganglion cells. This idea was based upon reports of others, indicating that AChE activity was very weak in other types of afferent nerve fibers.

The olivocochlear bundle[6,7] is a tract originating from the retro-olivary nucleus situated near the superior olivary bodies. The tracts run to the floor of the fourth ventricle where they decussate between the colliculi of the facial nerves and pass into the inferior divisions of the vestibular nerves. Passing through the saccular ganglion the bundle divides into three fascicles which, upon entering the spiral ganglion canal, are known as the intraganglionic fascicles. The fascicles course along the spiral ganglion from which fibers can be traced toward the organ of Corti. The precise termination of these fibers has not been determined.

We thought, if the AChE in the cochlea was contributed by the efferent bundle, destruction of the bundle should be followed by disappearance of the enzyme in the cochlea. Therefore, in operations upon cats we cut Rasmussen's bundle by incisions made in the right sulcus limitans 10 mm. from the obex. (Fig. 1.) After a lapse of seven to thirty-five days the cats were decapitated, both cochleas were removed and treated in identical fashion. The medullas were fixed, sectioned, stained with Sudan Black B, and mounted in Apathy's syrup.

Sections of the medullas and right cochleas showed satisfactory degeneration of

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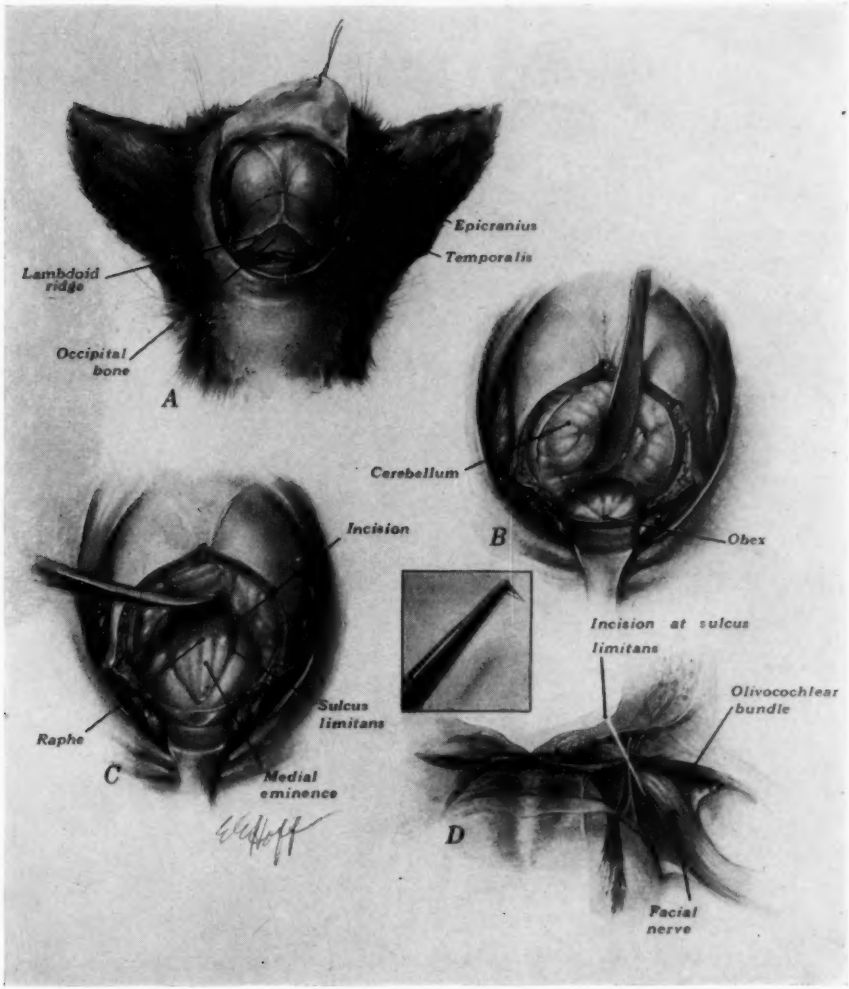

Figure 1

A. Posterior craniotomy approach to the posterior fossa.
B. Elevation of the cerebellum to expose the floor of the fourth ventricle.
C. and D. Location of incision to cut the olivocochlear bundle.

Rasmussen's bundle in seven out of eleven cats operated upon.

Fig. 2 shows the normal olivocochlear bundle and normal acetylcholinesterase stain in the cochlea, whereas Fig. 3, by comparison, shows in the experimental ear the degenerated bundle and decreased stain in the cochlea.

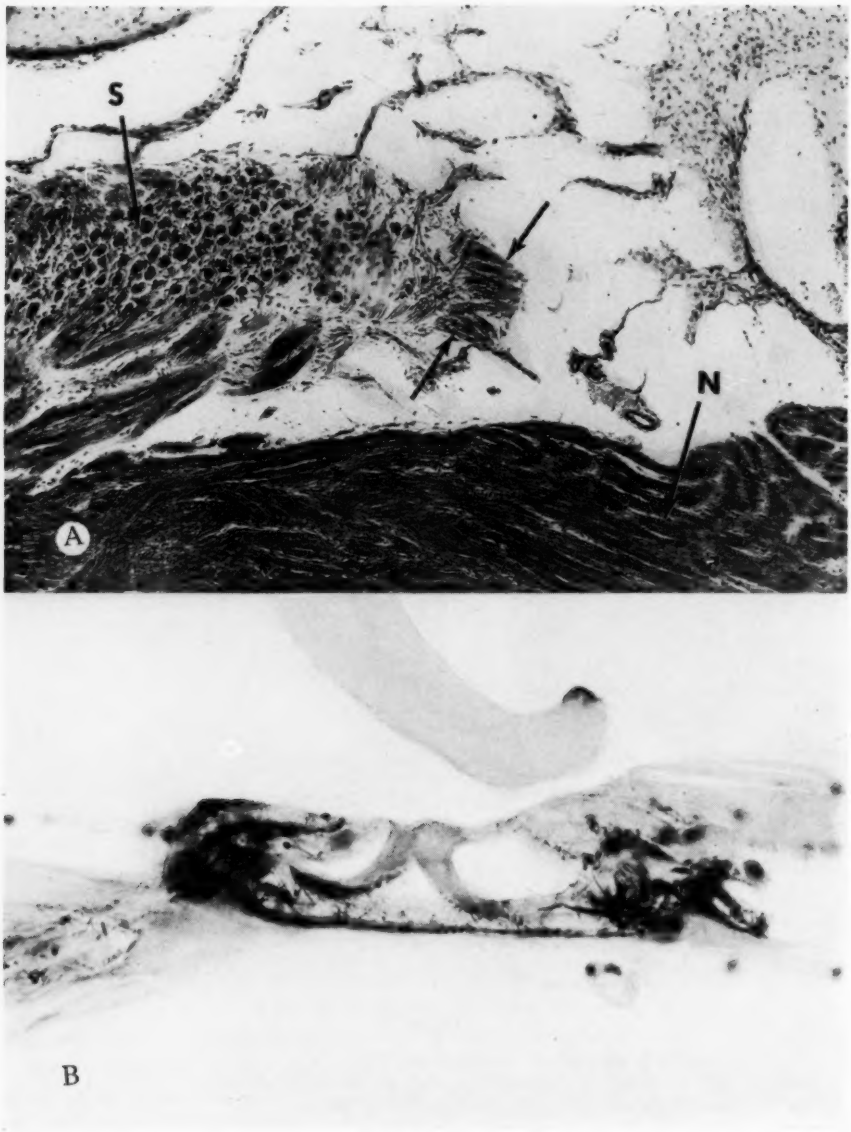

Figure 2

Photomicrographs from normal ear.

A. View in internal auditory meatus showing saccular ganglion (S), cochlear nerve (N), and olivocochlear bundle (between two arrows).

B. AChE stain in organ of Corti is normal.

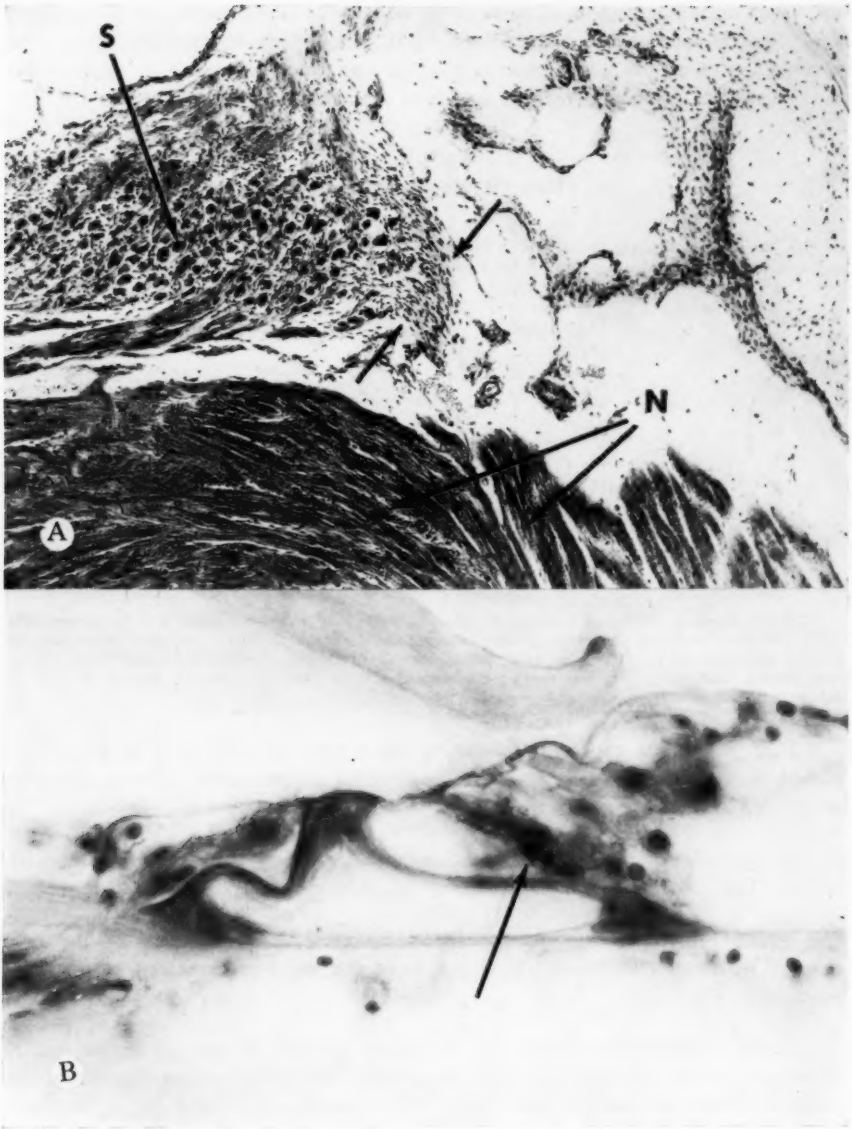

Figure 3

Photomicrographs from the right (experimental) ear of Cat sacrificed 14 days after cutting right olivocochlear bundle.

A. View in internal auditory meatus showing saccular ganglion (S), cochlear nerve (N), and degenerated olivocochlear bundle (between two arrows).

B. Only a small discrete deposit of stain (arrow) indicating AChE is present in region of first outer spiral bundle.

Seven of the eleven cats operated upon showed degeneration of Rasmussen's bundle, but in four the bundle remained intact. Those with degeneration of the tract revealed loss of copper sulfide stain in the organ of Corti, those with no degeneration revealed normal amounts of copper sulfide in their organs of Corti. (Table I.)

TABLE I

SECTION OF EFFERENT BUNDLE

Cat. No.	Survival Time Days	Degeneration Efferents	Decrease in Cochlear Stain for AChE
1	7	Great	Moderate
2	14	Great	Great
3	14	Great	Great
4	18	None	None
5	18	None	None
6	20	Great	Moderate
7	20	None	None
8	21	(Artefact)	Great
9	21	None	None
10	28	Great	Great
11	35	Great	Great

Table showing results of cutting the olivocochlear bundle on the right side in eleven cats. In the six ears in which the olivocochlear bundle was degenerated, there was also a decrease in cochlear stain for AChE. The four ears with a normal appearing olivocochlear bundle had normal stain density. The nerve was inadvertently avulsed from the internal auditory meatus of Cat 14 and was not available for study.

The densities of copper sulfide along the length of the organs of Corti were estimated and plotted graphically. The contrast in copper sulfide densities between unoperated and operated (right) ears for four cats can be seen in (Fig. 4.)

In another group of cats the right eighth cranial nerve was cut at the acoustic meatus. The cochleas of these animals also revealed loss of copper sulfide. (Fig. 5.)

A third group of cats was treated by injections of streptomycin in the right auditory bulla.[8] By this means the hair cells of the organ of Corti can be destroyed selectively. (Fig. 6.)

In the streptomycin treated ears we found that the density of copper sulfide representing AChE activity was not appreciably decreased even in regions of the organ of Corti denuded of hair cells. Since AChE was found to be markedly decreased in cochleas following successful section of their olivo-cochlear tracts in the medulla, but remained intact following degeneration of hair cells, we concluded that AChE in the cochlea depended upon the integrity of the olivo-cochlear bundle. The olivo-cochlear bundle must terminate in close proximity to the hair cells or the dendritic endings of the acoustic nerve.

The function of the olivo-cochlear tract has not yet been discovered; but the

tract appears to be a feedback pathway for impulses originating at a relay point (the retro-olivary nucleus of the superior olivary body) in the contralateral side of the medulla and ending upon the hair cells in the organ of Corti. There is reason

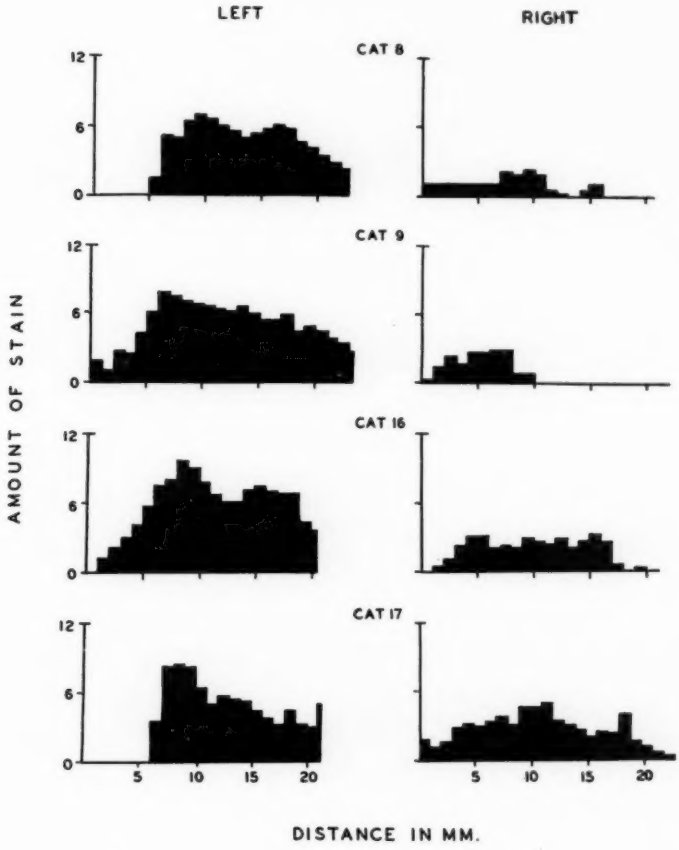

Figure 4

Charts showing relative amounts of stain in the cochleas of four cats in which the olivocochlear bundle was cut on the right side. The cochleas were graphically reconstructed and an estimate was made of the density of stain throughout the length of the cochlea. The stain was rated as being absent, light or dense, with values of 0, 1, and 2 respectively, for each of six structures and a total value given for the cochlear duct at each point where it was sectioned. On the ordinate is the stain density rating and on the abscissa the distance in millimeters as measured along the organ of Corti. In the normal left ear the concentration is greatest in the upper basal turn in about the 7 mm to 11 mm regions. The amount of stain diminishes rapidly from this region in a basalward direction, and in some ears is totally absent in the hood end of the cochlea. Although the stain diminishes progressively toward the apex, considerably more exists at the apex than at the base. The amount of stain is considerably reduced in the right ears which were deefferentized.

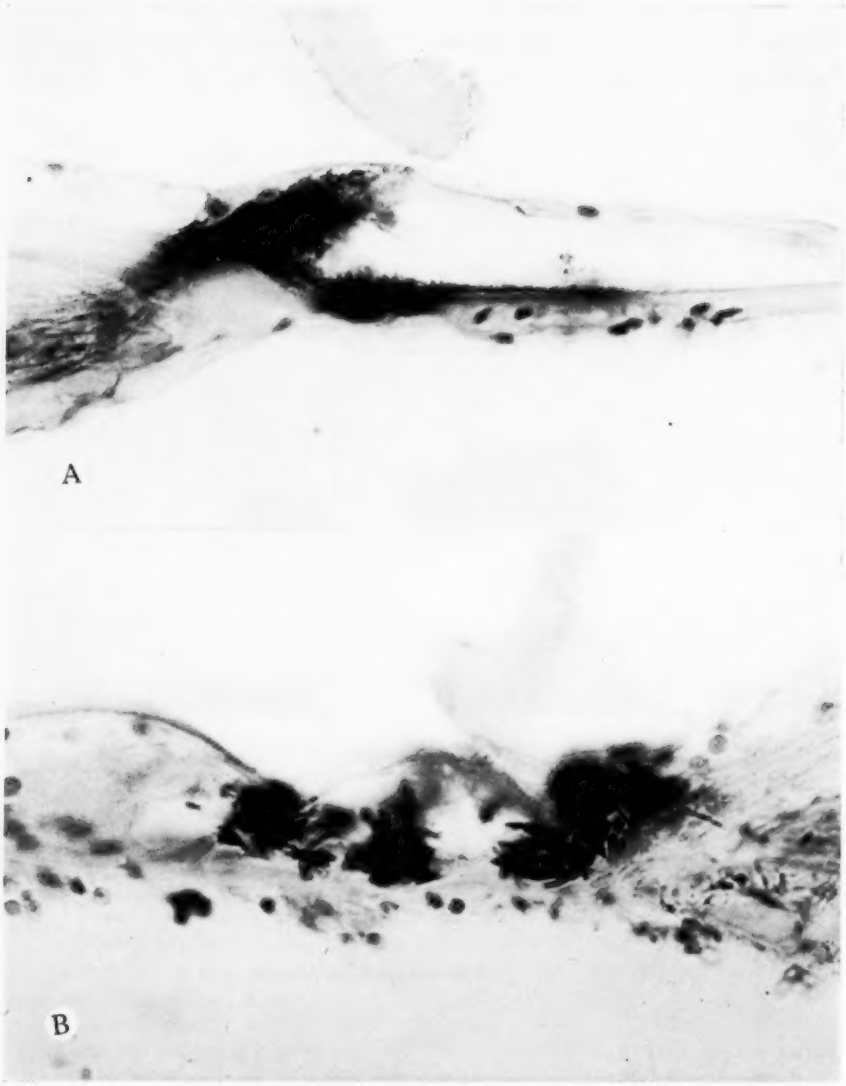

Figure 5

This animal was sacrificed thirty days after section of the right acoustic nerve.

A. Stain on nerve fibers in organ of Corti of left (control) ear.

B. Small deposit of stain in area of inner spiral bundle of right (experimental) ear. Normal hair cells.

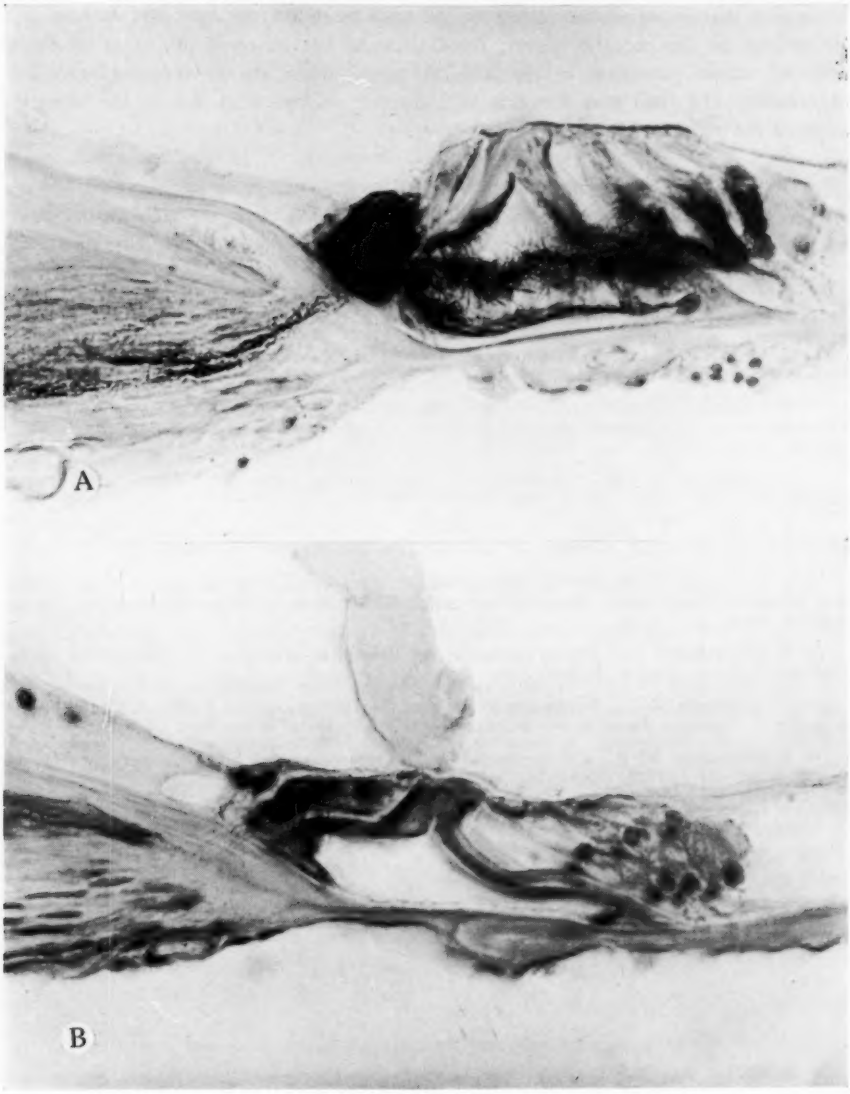

Figure 6

AChE remaining after loss of hair cells.

A. Cat sacrificed twenty days after injection of streptomycin sulfate into auditory bulla. There is severe atrophy of the organ of Corti but a dense concentration of stain exists in the region of the inner spiral bundle and on the basilar membrane.

B. Severe atrophy of organ of Corti but dense stain located in region of spiral bundles and tunnel fibers.

to believe that impulses transmitted by the tract modulate the responses of hair cells or endings of the acoustic nerves; for Galambos[9] has observed inhibition of sound induced action potentials in the acoustic nerve when the olivo-cochlear tract is stimulated. The tract may function in a manner analogous to that of the amacrine cells of the retina.

One can reason that impulses transmitted to the endings or paraterminal boutons of the olivo-cochlear fibers liberate acetylcholine, which alters the state of excitation of the endings of the acoustic nerves or the hair cells.

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THE MECHOLYL TEST; ITS VALUE IN DEPRESSIONS

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In recent years a great deal of attention has been directed toward the hypothalamus and the reticular formation in relation to the psychologic functions of the organism. Disturbances in the functions of these areas are evidenced by altered activity of the autonomic nervous system and of the psyche. Attempts have been made primarily by Funkenstein[1,2] and by Gelhorn[3], to establish a predictable relationship between the more readily observed and measured alterations of autonomic system functions, and the more elusive variations of the psyche utilizing the Mecholyl test.

The hypothalamus may be roughly located between the mammillary nuclei, the optic chiasma, the anterior commissure, and the inferior surface of the thalamus. In this general area there are a number of cellular masses which are not clearly separable, but which have been roughly divided into so-called nuclei. The function of each of these nuclei is not clearly understood, but one of the most widely accepted statements is that the posterior nuclei appear to be directly connected with the activity of the sympathetic portion of the autonomic systems, whereas the anterior nuclei appear to be more connected with the parasympathetic division. These nuclei are inter-connected and also are connected both afferently and efferently with the cortex, thalamus, and reticular core of the central nervous system.

Consciousness seems to require activation of the cortex not only through the specific afferent sensory system but also through (1) the reticular substance and (2) the hypothalamus. These lower systems regulate the degree of receptivity of the cortex permitting it to become aware of stimuli which would otherwise be subliminal or filter out stimuli so that the cortex is not overwhelmed and confused by a flood of stimuli. Thus it is these systems which control what we preceive and not the cortical sensory areas as previously thought.

Emotional responses are similarly controlled by these systems. The general outline of this feed-back circuit is sensory cortex — frontal cortex — hypothalamus — reticular substance — cortex. If any portion of this circuit is impaired, the quality of the emotional response is also impaired.

The hypothalamus and reticular substance are also indispensable for the formation of conditioned responses in two respects. Firstly, they tend to determine the level of excitability of the cortex. Areas of increased responsivity then tend to gather unto themselves other temporally occurring stimuli. Thus the conditioning stimulus such as the sound of the bell, will attract the simultaneously received primary stimulus, the sight of food. Secondly, conditioning occurs only when some emotion — fear, pleasure, etc. — is involved. As shown above these systems definitely affect the level of emotional responsivity. Thus one of the main learning techniques is closely related to the reticular substance and the hypothalamus.

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Since hypothalamic activity has been shown capable of (1) altering perceptions, (2) modifying responses, (3) modifying emotional reactions, and (4) determining the rate of learning conditioned responses, it would appear likely that gross behavioral changes would occur from any alteration in hypothalamic activity.

Since the posterior hypothalamic nuclei seem to be so closely connected with the activation of the cortex and also with the activation of the sympathetic portions of the autonomic system, Funkenstein devised a test purported to measure the state of reactivity of that area.[1] It has been well-established[3] that when the pressure in the sino-aortic area is lowered through mechanical or chemical means, increased sympathetic discharges ensue which have a tendency to counteract the experimentally induced hypotension. These discharges appear to be mediated through the posterior hypothalamic nucleus as, when that nucleus is inactivated by barbiturates or more permanently by high frequency lesions, the prompt return of blood pressure to the normal level does not occur. When this nucleus is intact, not only does the blood pressure return to normal, but there are other signs such as changes in pupillary size indicative of increased sympathetic autonomic nervous system activity. Likewise, if this nucleus is further stimulated by the local application of strychnine, not only does the blood pressure return, but does so more promptly and even overshoots the resting mark for some period of time. Thus to the subcutaneous injection of 10 milligrams of methacholine, the normally active posterior hypothalamic nucleus is postulated to cause the blood pressure to return to normal in about 10 minutes with possibly a very slight amount of secondary increase. Should this nucleus be in a state of increased excitation the blood pressure would return sooner, and a greater degree of over-reaction would follow. Should the nucleus be underactive, the blood pressure would return to the resting level much more slowly. Of course there are all gradations in between these three characteristic responses and arbitrary boundaries have been drawn. One method has been to plot the change in the blood pressure in millimeters of mercury against the time in minutes for 25 minutes. Five millimeters change in blood pressure is equal to one centimeter, and one minute is equal to one centimeter. The area of change is then measured. Should there be an increase of greater than 6.4 square centimeters it is classified as type I or hyper-reactive. If the change varies between $+6.39$ and -35.49, it is type II or normal. Should the decrease be greater than -35.5 square centimeters it is then classified as type III or hypo-reactive.

Clinically Funkenstein reported a positive correlation between individuals with type III (hypo-reactive) responses, and the beneficial result of electro-shock therapy in relieving their symptoms whether the condition was schizophrenia or depression. Pasquarelli[4] also reported a correlation between the type III responses and the presence of affect on one hand, and between the type III response and recovery from mental illness on the other hand. Neither of these correlations were as high as the one between the clinical estimate of affect and the recovery from illness. However Lotsof and Yobst[5,6] and also Sloane[8] reported no correlation between the type of response to methacholine and improvement following ECT. It was the purpose of this investigation to determine whether any correlation could be seen between the blood

pressure reaction to methacholine and the clinical response to therapy and also what effect ECT had upon the methacholine reaction.

PROCEDURE

In this study the mecholyl test was administered to 20 newly admitted white patients (14 women and 6 men) between the ages of 28 and 69 who had the symptom of depression. In 14 this was associated with a neurosis; in the remaining 6 five other diagnoses were indicated. Each patient had a private room on the 24 bed "open" psychiatric floor in a 1,112 bed general hospital. Six full-time senior psychiatrists and 3 residents care for these 24 patients thus permitting the most intensive of therapy. There is a special occupational therapy unit on the floor and psychologic and social service assistance is constantly available. With such intensive therapy the average stay of a depressed patient is less than three weeks. The sight of others recovering and going home enhances this positively oriented atmosphere and, exerts an unmeasurable force toward recovery so that the patients' responses cannot be attributed to ECT alone.

The test was administerd only by the author in order to avoid any variations due to technique or interpersonal relations. The patient was requested to remain quietly in his room after arising. Before breakfast was served the author visited him and requested he lie down until the blood perssure stabilized. Ten milligrams Mecholyl* was then injected subcutaneously and the blood pressure recorded for the next 25 minutes or longer. This was done a day or two after admission when the depression had been clearly recognized but no therapy had been yet begun. In seven cases the procedure was repeated after completion of their course of ECT to compare the responsivity before and after ECT.

The response to therapy was checked approximately one year after discharge and classified as follows:

1. Good recovery — depression relieved and patient essentially symptom free.

2. Recovered — relapsed — recovered. Patient did well during initial hospitalization, then had a return of his symptoms which responded either to psychotherapy or to further ECT until a good recovery was achieved.

3. Depression relieved — These were usually the psychoneurotics who had developed a depression in addition to their other symptoms. The therapy relieved the depression but the chronic neurosis remained symptomatic.

4. Slight improvement — The depression lessened so that patient could leave hospital but was still evident.

5. Essentially unchanged.

*The methacholine (Mecholyl) used in these experiments was kindly furnished by Merck, Sharp, & Dohme, West Point, N. Y.

RESULTS

The two individuals who had a type I reaction to methocholine did rather poorly. This is not surprising as both were quite neurotic, passive, dependent personalities. However, one did gain considerable relief of her depression. The clinical responses of the remaining seven Type II, and eleven Type III, reactors showed no correlation whatsoever (chart I). One of the most prominent Type III reactors (—89 square centimeter) showed no change while two of the best recoveries occured in Type II reactors (—9 and —22 square centimeter).

CHART I

Clinical response	No. Pts.	Type Mecholyl Response I	II	III
Good	5	0	1	4
Better, relapse, then final recovery	4	0	3	1
Depression relieved, other symptoms remain	4	1	1	2
Slight improvement only	4	1	1	2
Essentially unchanged	3	0	1	2

In those patients where the reaction was determined both before and after ECT the change in the area was calculated and charted against the degree of clinical response (chart II). In two cases there was essentially no change in the reaction although clinically the patients were considerably better. The patient showing the best clinical response went from —131 to —232 directly contrary to what would be expected from Gelhorn's thesis[3] that ECT acts as a mass stimulus to the entire brain but that the sympathetic system's responses over-balance the parasympathetic ones. Were this true ECT should produce a hastening of the blood pressure's return to normal. However, the relative strengths and balances of individuals' autonomic systems varies widely. Richter[9] observed that some persons flushed while others blanched during London air raids. Wolf[10] observed similar variations in the gastrointestinal system.

CHART II

Change in area (sq. cms)	—101	—52	—4	+8	+28	+70	+95
Clinical improvement	+4	0	+3	+4	+3	+3	+3

SUMMARY

The Mecholyl test was administered to 20 acutely depressed persons. Except for noting that those who have a Type I (hyper-reactive) response did more poorly, no correlation of prognostic significance was found. The rate of return of blood pressure to the resting level was altered by ECT but in no predictable direction and this had no correlation with clinical improvement. ECT and depression affect too many portions of the nervous system to permit a test purportedly measuring only hypothalamic activity to be of prognostic significance.

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EXFOLIATIVE CYTOLOGY IN THE CLINICAL EVALUATION OF GASTRIC ULCER

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GERALD FINE, M.D.,** AND ELIZABETH WATSON**

The application of conventional methods — radiographic examination of the stomach, gastric analysis, gastroscopy, and medical treatment as a test of healing — has resulted in good separation of benign and malignant ulcers. The study of exfoliative cytology has become well established in recent years and has been utilized to improve diagnostic accuracy in the patient with a gastric lesion.[1,2] The present study is an attempt to delineate the specific indications for the latter.

METHODS

The records of all patients who had cytology examination of gastric washings at Henry Ford Hospital through November 1, 1958 were reviewed. One hundred and four patients were selected because they had a final diagnosis of gastric ulcer or gastric malignancy. Seventy three had benign gastric ulcer. A patient was considered to have benign gastric ulcer if he had no recurrence of symptoms for 12 months (65 patients), or a diagnosis of benign gastric ulcer on a resected specimen (8 patients). Twenty two had carcinoma of the stomach and 1 Hodgkin's disease of the stomach all proven by tissue examination. Eight patients were felt to have benign ulcer but could not be classified because of unsatisfactory followup.

Cytology study was performed according to the technique of Rubin.[3] Seven mgm. of chymotrypsin B was added to 500 ml. of an acetate buffer of pH 5.6 and introduced into the stomach. The patient was rotated for 8 minutes and the fluid was withdrawn. The aspirated fluid was kept on ice, and was centrifuged and fixed promptly. An average of 6 slides per case were screened by an experienced cytotechnician and reviewed by a pathologist. Collection of fluid was done by a nurse in most cases.

RESULTS

Our accuracy in the diagnosis of gastric malignancy by the cytology technique is recorded in Table 1. Possible errors in diagnosis can be ascribed to several factors

Accuracy of Gastric Cytology in Gastric Malignancy

	Positive	Negative	%
First Washing	14	9	61
Second Washing	18	5	78

Table 1

which include the manner of collection, variation in clinical material, fixation of slides, and accuracy of interpretation.[4] Analysis of the 5 false negative results revealed that the collection of the exfoliated material was the most vulnerable part of the procedure. Two false negative results were obtained in patients with lesions at the

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esophagogastric junction. One of these patients had a normal esophagoscopy; and the other, an esophageal stricture that a string could not pass. The slides of the other three patients were studied repeatedly with out finding malignant cells. In each of these three cases gastric washing was performed only once and there was no opportunity to repeat the study.

The accuracy of each of the other methods in the diagnosis of benign and malignant lesions is presented in Tables 2 and 3. In tabulating the results the opinion

Accuracy of Other Methods in Gastric Malignancy

	Interpreted Malignant	Interpreted Benign	Not Done	% Correct Diagnosis
X-ray	19	4	0	82
Endoscopy*	9	2	12	82
Gastric Analysis	4**	12	7	25

*See Text
**No free acid even with histalog stimulation

Table 2

Accuracy of Methods in Proved Benign Gastric Ulcer

	Interpreted Malignant	Interpreted Benign	Unsatisfactory	Not Done	% Correct Diagnosis
X-ray	9	64	0	0	88
Endoscopy	3	16	13	41	50
Gastric Analysis	1*	66	0	6	98
Cytology	0	72	1	0	98

*No free acid even with histalog stimulation.

Table 3

of the radioloigst at the time of the initial examination was recorded. With few exceptions a single endoscopic study was performed in both groups. Four patients with carcinoma of the stomach had esophagoscopy and a biopsy was taken in 3 of these. One yielded malignant tissue, and the other two, normal esophagus. Forty-three patients had gastroscopy. Gastric analysis was interpreted as indicating a malignant lesion only if there was no free acid after histalog stimulation.

Diagnostic accuracy was improved by combining the results of the various tests. In the group of patients with gastric malignancy 20 patients had a correct diagnosis by conventional techniques. One of three patients diagnosed incorrectly by the latter combination was correctly diagnosed by cytologic study. The remaining two patients in this group were misdiagnosed preoperatively by all methods.

There were 6 patients who had benign gastric ulcers that were called malignant by a combination of radiographic examination, gastroscopy, and gastric analysis. Each of these was correctly diagnosed by the cytology method. Repeatedly negative gastric cytoiogy supports a diagnosis of benign gastric ulcer.

DISCUSSION

The indications for gastric washings are listed in Table 4. The single instance of

Indications for Gastric Cytology

1. All gastric ulcers in the antrum, on the greater curvature, or in the fundus of the stomach.
2. Any other lesion in any part of the stomach if malignancy is a consideration.
3. Confirmatory histologic diagnosis of malignancy to avoid operation where chemotherapy or radiotherapy are the only modes of therapy considered.

Table 4

gastric carcimona diagnosed as a benign ulcer by conventional means and as a malignant lesion by cytologic study was in the gastric antrum. Seven of the 9 cases of benign gastric ulcer diagnosed incorrectly by x-ray were in the gastric antrum; 1 was on the greater curvature and 1 was on the lesser curvature in the body of the stomach. These figures assume even greater importance if one considers that of a total of 73 benign ulcers 40 were on the lesser curvature in the body of the stomach, 30 were antral ulcers, and only 3 were on the greater curvature. It is evident that the radiologist makes most of his errors on antral, greater curvature and fundic lesions.

The endoscopist has difficulties in the same anatomical areas. Of the two gastric malignancies diagnosed incorrectly one was in the fundus and the other in the distal 2/3 of the stomach. Two of the three benign ulcers mistaken for tumor by the endoscopist were on the lesser curvature and one was in the antrum. In addition the endoscopist often does not see lesions in these areas. This is shown by the fact that 7 of 13 unsatisfactory gastroscopic examinations were in patients with antral lesions, 1 with a greater curvature and 5 with lesser curvature lesions. Because antral ulcers are so difficult to see adequately, gastroscopy is often not attempted in the presence of ulcer in this location. However, gastroscopy should be performed whenever feasible in cases where the nature of the ulceration is in doubt.

In summary then, the conventional techniques are seldom wrong in the diagnosis of lesser curvature ulcers in the body of the stomach. In this situation routine gastric cytology is not necessary.

Gastric cytology assumes special importance in the presence of gastric ulcers in the antrum, on the greater curvature and in the fundus.

SUMMARY

Exfoliative cytology study of gastric washings was performed in patients with gastric ulcer and gastric carcinoma. The indications for gastric cytology in the patients with gastric ulcer were noted and are summarized in Table 4. It is of utmost importance that *all* diagnostic means are utilized in attempting to solve the question — "benign or malignant"?

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THE CONTROL OF POSTOPERATIVE PAIN BY THE USE OF LOCAL ANESTHETIC PUMPS

JAMES BARRON, M.D.*

Pain of some degree is always present in postoperative wounds. Fear of this pain frequently causes the patient to postpone elective surgery or to delay in seeking surgical care for the more acute emergencies. The painful wounds may lead to a marked reduction in vital capacity in certain areas of the body. Morphine and other analgesics have had a long and almost universal use to reduce respiratory depression and frequently will complicate the postoperative care of elderly patients.

Small plastic tubes placed in the chest wound at the time of surgery were suggested by Blades and Ford in 1950.[1] They injected 2 cc. of 1% or 2% procaine through these tubes every three hours. They and others used this method with good results. This method has not been widely used. This lack of widespread use has no doubt been due to many factors such as: time-consuming injections every three hours, brief duration of procaine anesthesia and the potential admission of bacteria by the numerous injections.

The recent introduction of new local anesthetic drugs with quicker action and longer duration when compared to procaine has not removed the many undesirable features of intermittent injections. In an effort to correct this, we began the use of small local anesthetic pumps which could be included in the dressing or held in place with strips of adhesive tape. (Fig. 1) These pumps have been made to

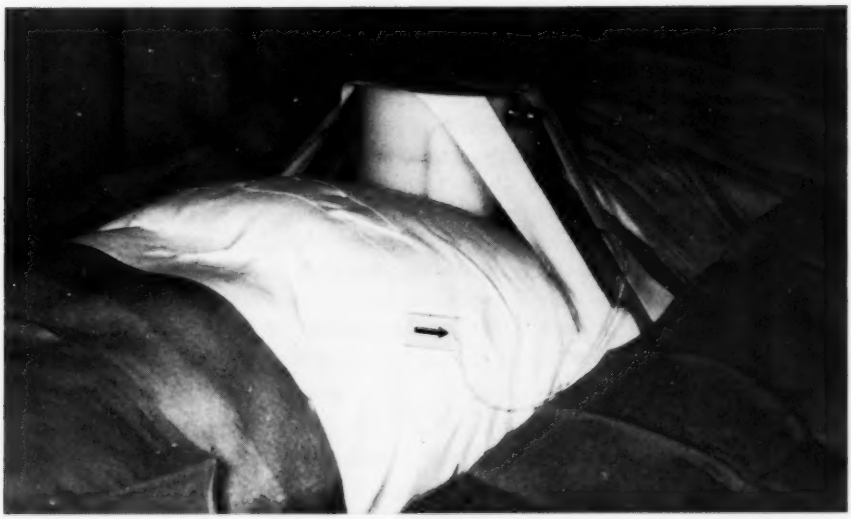

Figure 1

Arrow points to small plastic tube brought out through dressing. The local anesthetic group is taped to the patient. The new models will be smaller and much easier to incorporate in the dressing. The basic principle of this pump has been used for many years for other purposes.

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contain enough local anesthetic solution to run for at least 24 hours. Little models of our tube feeding pump run by an electric motor were first used. However, the electric cord added certain potential problems and hazards. Spring wound mechanisms so far have been too heavy and bulky and have lacked sufficient power. The most recent pump consists of a nylon or stainless steel tank divided into two chambers by a rubber diaphragm. The pressure to operate the pump is supplied by introducing oxygen or CO_2 in one tank with the local anesthetic solution occupying the other side. The rubber diaphragm is necessary to prevent the escape of gas into the wound. The delivery rate of the solution is governed by a needle valve and the gas pressure. No electric cord is required. The outside shape is now being changed to that of a small elongated cylinder (resembling a hot dog bun) which makes the pump much easier to tape in place.

Up to the present, pumps have been used mostly for upper abdominal wounds which are well recognized for their postoperative discomfort and reduction in vital capacity. Small plastic tubes have been placed in the wound depths at the time of closure. Fine silk and plain catgut sutures have been used to hold these tubes in place. In these cases, we have attempted to place the deep tube openings near the main nerve trunks supplying the area of the wound.

The individual reaction to pain is subject to wide variation. The use of local anesthetic in the wound has seemed to give a definite significant decrease in the postoperative use of Demerol, morphine and other similar analgesics. Many of the patients will request postoperative medication for headache, nervousness and insomnia rather than for pain in the operative site. Postoperative breathing and ambulation have shown definite improvement in the majority of the patients. Many of the cases have seemed to exhibit a decrease in postoperative abdominal distention and nausea.

For most cases, we have used 1% and 2% Xylocaine. The amount has averaged from 30 to 50 cc. every 24 hours through each tube. We have not observed any undesirable effects on the healing of wounds. The pumps have seemed to give the most benefit during the first 48 to 72 hours when one would expect the major portion of postoperative wound discomfort. We are now planning an extensive controlled program as a cooperative effort with our Department of Anesthesia. The method is simple and is not time-consuming. We have had sufficient experience to predict that postoperative wound discomfort in most patients can be definitely decreased. The majority of patients are indeed grateful for the help in reducing the postoperative wound discomfort.

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ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

***STUDIES ON THE MECHANISM OF AMINONUCLEOSIDE-INDUCED NEPHROSIS IN THE RAT.** P. BARTLETT, B. GERULAT, AND S. SHELATA. Fed. Proc. 18:186, 1959.

Structural similarity of adenosine and the aminonucleoside, 6-dimethylamino-9-(3'-amino-ribofuranosyl)-purine, suggests that the mechanism by which the latter induces nephrosis in the rat might involve interference with adenosine metabolism at the nucleoside, nucleotide, or nucleic acid level. Results of initial studies of this aspect of the metabolism of aminonucleoside labeled with tritium by the Wilzbach procedure form the basis of the present report. Both kidney and liver tissue, obtained from normal adult rats rendered nephrotic by daily subcutaneous injections of 1.5 mg. labeled aminonucleoside (10 microcuries per mg.) per 100 gm. body weight for a period of 10 days, have been processed by the procedure of LePage and Heidelberger for the isolation of the barium salts of RNA and DNA. Under these conditions no incorporation of radioactivity was apparent in either kidney RNA or kidney and liver DNA. Our measurements do, however, indicate the presence of the isotope in liver RNA. Isotope was also found in 4% perchloric acid extracts of kidney and of liver tissue made prior to removal of phospholipids and isolation of the nucleic acid fractions. Work now in progress should enable us to determine the chemical nature of the radioactivity of the perchloric acid extracts and the liver RNA.

***EFFECT OF DIETARY BILE ACIDS ON IN VIVO CHOLESTEROL METABOLISM IN THE RAT.** W. T. BEHER AND G. D. BAKER. Proc. Soc. Exper. Biol. & Med. 98:892, 1958.

A 3-week period of feeding a diet containing 0.5% cholic acid did not alter serum and adrenal total cholesterol levels. However, a slight but significant increase in liver total cholesterol was observed. Dietary dehydrocholic acid had no effect on serum, liver or adrenal total cholesterol levels. Cholic acid increased serum bile acid had no effect. Dietary cholic acid reduced rates of synthesis and mobilization of cholesterol in both liver and adrenal. Dehydrocholic acid produced similar results but to a lesser degree. Accumulation and mobilization of serum cholesterol were retarded by dietary cholic acid, and slightly by dehydrocholic acid.

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RELATIONSHIP OF LITTLE'S DISEASE TO PREMATURE BIRTH. J. A. CHURCHILL. A.M.A. J. Dis. Child. 96:32, 1958.

A study of 76 patients with Little's disease revealed that they could be segregated into two groups having relatively distinct clinical characteristics. One group, called simple spastic diplegia, was found to be composed of persons who, for the most part, had had low birth weights. In sharp contrast, low birth weight was not a prominent feature of the other group, which was called complex diplegia. The significance of low birth weight (prematurity) in the pathogenesis of simple spastic diplegia is discussed.

MYXOMA OF THE RIGHT ATRIUM, WITH VARIABLE RIGHT-TO-LEFT SHUNT; CLINICAL AND PHYSIOLOGIC OBSERVATIONS AND REPORT OF A CASE WITH SUCCESSFUL OPERATIVE REMOVAL. E. O. COATES, JR., AND ELLET H. DRAKE. New England J. Med. 259:165, 1958.

A case myxoma of the right atrium presenting unusual diagnostic features is reported. The demonstration by appropriate arterial-blood studies of a right-to-left shunt (through a patent foramen ovale), varying with change in position, provided an important clue to the correct diagnosis. Findings at cardiac catheterization closely resembled those of Ebstein's syndrome. A definitive diagnosis was obtained

by angiocardiography. Successful surgical removal of the tumor was accomplished by open-heart operation, using a pump oxygenator and a stopped heart. In view of the fact that cure is now possible, the detection of intracardiac myxomas during life has become of major importance.

PHILOSOPHY OF THE MANAGEMENT OF CORONARY OCCLUSION. L. C. DICKSON, JR. Postgrad. Med. 24:3, 1958.

The physician managing a patient with a coronary occlusion will be wise to make an honest estimate of the restrictions necessary and try to avoid those that are unnecessary and arbitrary. He should issue the restrictions to the patient, with explanations as to why they are necessary. The patient will take them with much better grace from a doctor than from nurses, aides, orderlies or, in some instances, even from the junior staff members. If the patient is harboring hostility, he should be given a chance to vent his feelings. A leading remark, such as, "All this instruction as to what you can and can't do must be making you pretty mad," often will open the floodgates and allow the patient to relieve himself of stored-up tension. It is important to remember that the patient detests helplessness, and an under-

standing and tolerance of his negative feelings in the catastrophic situation of myocardial infarction may make a real difference in his immediate progress and ultimate prognosis.

LEIOMYOSARCOMA OF THE NASOPHARYNX. G. D. DOBBEN. A.M.A. Arch. Otolaryngol. 68:211, 1958.

A previous report of a leiomyosarcoma of the nasopharynx cannot be found in the medical literature. Geschickter, in classifying sarcomas of the nasopharynx, listed two cases as myosarcomas. One of these was a rhabdomyosarcoma, and he has illustrated this tumor. The second case, which is listed as being myosarcoma, has no further explanation. An original case report of a leiomyosarcoma of the nasopharynx has been presented with the radiological and histological findings.

INTERMITTENT HYDRARTHROSIS (PERIODIC BENIGN SYNOVITIS). D. C. ENSIGN AND J. W. SIGLER. Postgrad. Med. 24:30, 1958.

We can only express our own thinking on this fascinating clinical picture by saying that intermittent hydrarthrosis or periodic benign synovitis is a condition which we often suspect, seriously consider, and occasionally diagnose; however, we rarely find it in cases which are thoroughly studied and systematically followed. Like the other instances of periodic disease, its cause is still shrouded in mystery. Again quoting from an authority of the past, we conclude with the opening sentences from the discussion by Moore which was the first article in English on this subject, published 94 years ago: "The subject of periodicity, or the tendency manifested by certain phenomena of life to recur after equal or nearly equal intervals of time, is still one of the curiosities of medical science. It has been often observed, yet not explained."

THE IMMOBILIZATION OF FRACTURES. J. L. FLEMING. Indust. Med. & Surg. 27:410, 1958.

A famous surgeon who, when asked how long a certain fracture should be immobilized, said "until it is healed." The statement, "until it is healed," is essentially correct; its only fault is its incompleteness. Healed for what? Weight-bearing or just to support the weight of a distal phalanx? For a sitting job or for hopping freight trains? Healed for whom? A child or an octogenarian? An athlete or an executive? This paper emphasizes the temporal relationship between immobilization and motion as they vary with the location of the injury and with the many imponderables inherent in the patient. A planned approach, specifically designed for the individual patient, will afford the largest number of successful results with the smallest number of permanently disabled patients.

*DIABETOGENIC EFFECTS OF GROWTH HORMONE; ROLE OF THE ADRENALS IN NITROGEN LOSS. O. A. GAEBLER, R. GLOVINSKY, T. VITTI, AND T. G. MASKALERIS. Diabetes 8:57, 1959.

A highly purified bovine growth hormone preparation was tested in normal and depancreatized bitches. In normal animals, its nitrogen storing action was similar to that of other purified growth hormone preparations; in depancreatized animals, the diabetogenic effects were very severe, despite absence of noteworthy amounts of corticotropin or thyrotropic hormone. Induction of nitrogen storage in the depancreatized dog with the present growth hormone preparation did not occur unless the dose of insulin was greatly increased, thus confirming our previous findings. The role of insulin in this connection is briefly discussed. The nitrogen loss produced by growth hormone in depancreatized dogs, which was prevented by adrenalectomy in earlier experiments, is readily reproduced with corticotropin or hydrocortisone; it may therefore be mediated by the adrenals. Unfavorable effects of growth hormone on carbohydrate utilization in depancreatized dogs, which were reduced but not prevented by adrenalectomy in earlier experiments, could not be reproduced with corticotropin or hydrocortisone. Prolonged pretreatment of a depancreatized dog with hydrocortisone did not prevent occurrence of severe glucosuria when growth hormone was also given. It did cause wild excitement and polydipsia, without noteworthy glucosuria.

LABORATORY IDENTIFICATION AND CLASSIFICATION OF STAPHYLOCOCCI. J.E. GREER. Am. J. M. Tech. 24:390, 1958.

The current prevalence of nosocomial infections and the importance of the staphylococcal problem make the rapid and accurate identification of pathogenic staphylococci a necessity. The important characteristic for laboratory diagnosis such as production of coagulase, *alpha*-hemolysin, and mannitol fermentation are given. Media for staphylococci are described. Phage typing is, of course, the final step in the labeling of pathogenic staphylococci. It is a test for the susceptibility of bacteria to virus infection. It can show two strains to be different, or that they be identical. It cannot prove two strains to be from identical sources. Phage results may be obtained from various typing centers, but cultures should not be sent without performing all the previously mentioned tests and forwarding the results, together with other pertinent information, along with the culture.

*From the Edsel B. Ford Institute for Medical Research.

NEOMYCIN SUSCEPTIBILITY FOR DIFFERENTIATING COAGULASE-POSITIVE FROM COAGULASE-NEGATIVE STAPHYLOCOCCI. J. E. GREER AND R. R. MENARD. Antibiotics Annual 1957-58, p. 149.

A study of 814 coagulase-positive and 336 coagulase-negative staphylococci has shown neomycin susceptibility and the coagulase reaction to be correlated in 800 (98.3 per cent) of the coagulase-positive and 310 (92.3 per cent) of the coagulase-negative staphylococci. This offers a method of differentiation similar to the bacitracin differentiation of group A from other beta-hemolytic streptococci. The effect of various techniques and commercial products was also studied.

NUMERICAL DESIGNATION OF STAPHYLOCOCCAL ANTIBIOGRAMS. J. E. GREER. Antibiotics Annual 1958-59, p. 881.

Several workers have reported the use of antibiograms in identifying strains of staphylococci. Such use is increasing, for antibiograms are clinically essential and are epidemiologically useful where phage typing is not available. The accuracy of the antibiograms in the identification of strains may be increased by extending the list of antimicrobial agents used (barring similar modes of action and cross resistance), but the number of possible antibiograms increases exponentially ($C = 2^n$). Thus, with only five antibiotics used there are 32 possible antibiograms. The naming of all the antibiotics used, however, plus stating the reaction of the bacteria to each antibiotic, is cumbersome whether written or spoken. A scheme is herewith proposed for a numerical designation of antibiograms.

DENTISTRY'S ROLE IN INTERDEPARTMENTAL HOSPITAL RELATIONS. F. A. HENNY. J. Oral Surg. 16:285, 1958.

Dentists are an integral part of the total health team and have much to contribute to the care of hospitalized patients. Because of the increasing quality of dental education, it is anticipated that dentistry will play an increasing part in hospital organizations. To meet these responsibilities and to produce an ever higher level of quality of patient care, dentistry long ago established special fields of interest and study which today are the recognized dental specialties. Basically these include oral pathology, oral roentgenology, orthodontics, prosthodontics, pedodontics, dental anesthesiology, periodontics, oral surgery and dental research, in addition to the broad field of operative dentistry.

HIGH-POTENCY PROGESTATIONAL AGENTS IN HUMAN PREGNANCY. C. P. HODGKINSON, E. J. IGNA AND A. P. BUKEAVICH. Ann. New York Acad. Sc. 71:753, 1958.

Sixty-one obstetrical patients, whose early pregnancies were complicated by uterine bleeding, presumably of decidual origin, were treated with 17*a*-hydroxyprogesterone caproate and 17*a*-ethynyl-19-nortestosterone. In all, 63 patients were treated, but 2 were eliminated because their bleeding episode resembled that of implantation, and treatment was begun after bleeding had spontaneously ceased. This report includes only those patients whose therapy was initiated during the phase of active bleeding and in whom the clinical diagnosis of threatened abortion had been made. The results were appraised according to the apparent influence of the drugs upon (1) total pregnancy salvage, (2) duration of gestation, and (3) the dynamics of abortion.

HIGH POTENCY PROGESTERONE DRUGS AND THREATENED ABORTION. C. P. HODGKINSON, E. J. IGNA AND A. P. BUKEAVICH. Am. J. Obst. & Gynec. 76:279, 1958.

In threatened abortion characterized by active uterine bleeding, a comparative appraisal was made of the influence of two high-potency progestational agents upon: (1) total pregnancy salvage, (2) duration of gestation, and (3) dynamics of abortion. In the luteoid-treated group the pregnancy salvage was 39.4 per cent; a tendency to early delivery was noted in 40 per cent of the patients; and the dynamics of abortion were delayed for 4 weeks or longer in 46 per cent of patients who aborted. These results were contrasted with those in a control group of 297 patients evaluated by similar standards in which the pregnancy salvage was 15.5 per cent and the delayed abortion rate 3.36 per cent. The potential pregnancy salvage for obstetrical patients who have active bleeding during early pregnancy was adduced to be 46.8 per cent. On this basis 84 per cent of the salvageable pregnancies were preserved by the luteoid agents.

OBSTETRIC HEMORRHAGE. C. P. HODGKINSON. J. Michigan M. Soc. 57:988, 1958.

Hemorrhage, for this presentation, is defined as abnormal bleeding from the internal pudendal vascular system, including the utero-ovarian axis, incident to or as the result of pregnancy and its cognate functions. It occurs for three reasons: (1) a break in the continuity of the vessel walls; (2) lessened efficiency of the mechanical hemostatic power of the myometrium; or, (3) deficient blood coagulation.

The treatment of obstetric hemorrhage should be preplanned and aggressively executed. Therapeutic efforts can be categorized into three general disciplines: emergency, diagnostic, and definitive. Definitive therapy depends on precise diagnosis of placenta praevia, poorly contracted uterus, hypofibrogenemia, or one of the many indications for surgical intervention.

COMPLICATIONS OF LEFT HEART CATHETERIZATIONS USING THE RIGHT TRANSTHORACIC APPROACH. D. KAVANAGH-GRAY AND E. H. DRAKE. Am. Heart J. 56:143, 1958.

We have reported the complications encountered during our series of left heart catheterizations. Of the 113 patients catheterized, hypotension developed in 3, sufficient chest pain to require analgesics was present in 19, hemoptysis appeared in 2, and routine, 24-hour chest roentgenograms revealed air or fluid in a pleural cavity in 8. In 3 instances, major complications have occurred in the form of embolic phenomena and cardiac tamponade. There have been no deaths. The incidence of complications has been significantly higher in cases in which the left atrium was not entered on the first attempt. It has been our impression, and that of other investigators, that puncturing the base of the aorta carries the greatest risk. The safety of the procedure, as carried out here, compares favorably with that of other investigators. It is our conclusion, therefore, that left heart catheterization, utilizing the right transthoracic approach to the atrium, is sufficiently safe to use in cases of diagnostic problems involving the aortic or mitral valves.

NEUROLOGIC MANIFESTATIONS OF MYXEDEMA. S. N. NICKEL AND B. FRAME. Neurology 8:511, 1958.

The present study has demonstrated that the nervous system in patients with myxedema is profoundly affected. The intellectual deterioration and the organic mental syndrome have received major emphasis for many years, but more recently there has been interest in the occurrence of coma in myxedema as attested by the many individual case reports in the literature. The occurrence and extent of peripheral nerve involvement in myxedema remain unsettled. Although the abnormal reflexes in myxedema are quite striking, the changes are not those usually seen in peripheral neuritis. Sufficient knowledge is available to postulate mechanisms of action for the neurologic manifestations of myxedema. One of the predominant features in the disease is the tendency for myxedematous collections to occur in various tissues throughout the body. It is most commonly seen in the subcutaneous tissue, especially about the eyes, but also occurs in serous cavities such as the pericardium and pleura. Some of the neurologic signs of myxedema could result from a similar interstitial

accumulation of myxedematous material in the nervous system. From the evidence gathered in this study, neurologic manifestations form a prominent part of the clinical syndrome in myxedema. It is felt that, with closer observation, these changes will be found to occur more often than heretofore emphasized.

ENDOMETRIOSIS AND INFERTILITY. J. P. PRATT. Internat. J. Fertility 3:151, 1958.

Estimation of the incidence of endometriosis depends upon when and by whom the diagnosis is made. Most of the reported cases of this disease have been observed in a special group of women who consulted a physician for a specific complaint. For this reason, they do not represent a cross section of the general population. The incidence of infertility is likewise elusive. Mere association of endometriosis and infertility is not satisfactory evidence that a causal relation exists. The symptoms of endometriosis vary with the location of the condition, because the symptoms are an expression of the reaction of the host tissue. The management of endometriosis is highly individualized. Conservatism is emphasized.

PHENPROCOUMON (MARCUMAR) I. AN AGENT FOR SHORT-TERM ANTICOAGULANT THERAPY. E. M. PRIEST AND H. G. PAULI. Am. J. Cardiol. 2:61, 1958.

One hundred and sixty patients received short-term anticoagulant treatment with phenprocoumon (marcumar). The effects of different initial doses of phenprocoumon were studied in 134 cases. Phenprocoumon proved to be a potent anticoagulant. Thirty or 36 mg of phenprocoumon produced the desired hypocoagulability of the blood as promptly as an initial dose of 51 mg, when these doses were followed on the second and third day, depending on findings in the Quick test, by doses which ranged from 0 to 9 mg. After therapeutic levels (prothrombin complex time 25 to 35 sec) had been reached, these were maintained with daily phenprocoumon doses of usually 3 or 4.5 mg. Both low and excessively high prothrombin time values were only rarely encountered with this dosage plan. Thus, in general, the desired depression of the blood clotting mechanism was easily maintained. The incidence of hemorrhagic complications was 3.75 per cent. Vitamin K_1 (mephyton or konakion) was an effective antagonist against undue depression of the blood clotting mechanism. These findings were compared with those reported by the original Swiss workers and by American and British students. It is concluded that phenprocoumon is an effective agent for short-term anticoagulant therapy and that selected therapeutic prothrombin levels can be maintained with comparative facility.

PERCEPTIVE HEARING LOSS. H. F. SCHUKNECHT. Laryngoscope 68:429, 1958.

Perceptive hearing loss here refers to that type due to disorders of the auditory pathways and cortex which is in accordance with the recent terminology suggested by the Committee for Conservation of Hearing of the American Academy of Ophthalmology and Otolaryngology. No one has yet evolved a completely clear concept of the psycho-acoustic manifestations resulting from lesions of the auditory pathways and centers. It is already apparent, however, that such lesions result in losses of intelligibility, varying from the mildest, detected only by special discrimination tests, to severe auditory aphasia. I am certain, however, that further physiological experimentation and clinical study will provide a better basis for the regional and functional diagnosis of disorders involving the auditory pathways.

*THE STRUCTURE OF SCHMIDT'S ALUMINUM HYDROXIDE GEL. P. SOUSZ SANTOS, A. VALLEJO-FREIRE, J. PARSONS AND JOHN H. L. WATSON. Experientia 14:318, 1958.

Aluminum hydroxide gels are used as adsorbents for proteins, enzymes, and viruses, particularly for preparing vaccines. By x-ray diffraction and electron microscopy it is shown that the gel aluminum hydroxide (SCHMIDT'S gel) is composed of particles, different by reason of their structure, morphology and dimensions to those of WILLSTATTER'S C-gamma gel, but similar to those which compose WILLSTATTER'S C-Beta gel.

RENAL DISORDERS AND DIABETES MELLITUS. F. W. WHITEHOUSE. Postgrad. Med. 24:54, 1958.

A number of renal complications associated with diabetes mellitus have been discussed, including glycogen nephrosis, acute and chronic pyelonephritis, necrotizing renal papillitis and diabetic nephropathy. Only assiduous care of the diabetes throughout his life can prevent or postpone these serious complications in the diabetic patient. Hence, good control is mandatory for the prevention of pyelonephritis. An earlier and higher incidence of diabetic nephropathy in the poorly controlled diabetic also has been demonstrated. When significant degenerative lesions have occurred, the progressively downhill course is difficult to halt. The patient must be not only encouraged during these months and years of trial but also kept as symptom-free as possible. Future advances in the knowledge of the nature of diabetes and its complications will help improve our over-all care of the diabetic patient.